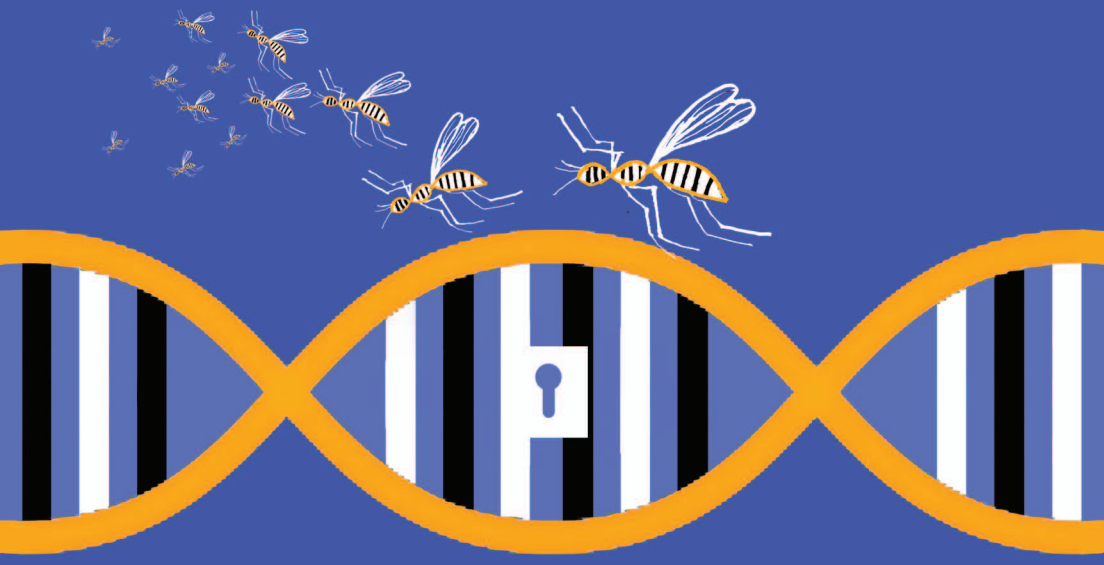

Gene Drives

Legal and Regulatory Issues

Lim Li Ching and Lim Li Lin

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Summary

There is an urgent need for effective international and legally binding regulation of gene drive organisms (GDOs). Existing biosafety rules, established for 'conventional' genetically modified organisms (GMOs), are deficient and not fully equipped to manage the unique risks of GDOs. With GDOs, spread and persistence are their *raison d'être*, posing different legal and regulatory challenges, because of their high potential to spread beyond national borders, particularly in the case of GDOs containing 'global' gene drives.

Our review of existing instruments and processes relevant to gene drives and GDOs shows that there are serious gaps. In our assessment, the Convention on Biological Diversity (CBD) and its Protocols, whose aims include the protection of biological diversity, whose scopes include GDOs and which have begun substantive work specific to GDOs, are currently the best home for their international governance.

We consider the following elements as fundamental in a legal and regulatory regime for GDOs:

- Strict contained use standards specific to GDOs to regulate its laboratory research, as well as strict containment measures for transport
- Joint decision-making, in terms of operationalising prior informed consent for all potentially affected countries of a particular environmental release
- Effective measures for dealing with unintentional transboundary movements

- Genuine public participation and obtaining the free, prior and informed consent of indigenous peoples and local communities
- Adapted risk assessment and risk management approaches for GDOs, including acknowledgment when such approaches are not possible
- Full assessment of socio-economic impacts including ethical concerns
- A technology assessment approach, including consideration of alternatives
- Rigorous monitoring and detection
- Stringent liability and redress rules

These elements are not fully in place and urgent efforts need to be undertaken to ensure they are translated into effective rules that are binding on all countries in order to remedy the serious gaps identified, *before* any release of GDOs is even contemplated. The 2018 decision and previous related decisions of the Parties to the CBD on GDOs make a start in this direction. They establish precautionary obligations that Parties should comply with before considering any GDO release, and to which the United States – a non-Party – and any GDO developer should also adhere in good faith.

To allow for the space and time to put in place legally binding governance arrangements at the international level, which should include the establishment and operationalisation of the elements identified above, the following are critical steps forward in the interim:

- There should be no intentional releases into the environment, including field trials, of any GDO
- There should be strict contained use standards applied to existing research and development in the laboratory, as well as strict measures for any transport of GDOs, to prevent escape
- Monitoring and detection for unintentional releases and unintentional transboundary movements of GDOs have to be conducted during this period, with emergency response plans in place
- International rules for this period of constraint, including for their enforcement and for liability and redress should there nevertheless be damage, must be effectively operational, including at national level

Chapter 1

The Need for Specific and Effective Laws and Regulation

A gene drive system is designed to purposefully spread genetic modifications through populations, with species-wide and ecosystem-level impacts, as well as to persist, which points to the likely irreversibility of those impacts (Heitman et al. 2016, 174). Even if releases are halted, spread of the genetic modifications, which may have unanticipated adverse effects, will almost certainly continue. Thus, the very characteristics that make organisms containing engineered gene drives or gene drive organisms (GDOs) attractive for development also require specific consideration of the risks unique to this technology. Gene drives that are designed to suppress populations could potentially result in population or species extinction, making this subset of particular concern.

While GDOs are also genetically modified organisms (GMOs), for which our collective experience is largely confined to agricultural crops in cultivated systems, with gene drive organisms there are novel conceptual and biological differences that pose particular challenges for regulation (Simon et al. 2018). The depth of this new technological intervention capability is such that "humanity has no experience engineering systems anticipated to evolve outside of our control" (Esvelt and Gemmell 2017, 5).

Some of the features of GDOs that distinguish them from 'conventional' GMOs include their purposeful spread and persistence. With GMOs, the intention, at least, has always been to prevent spread of the modified genes and to confine their effects, with gene flow or contamination, for example, being one of the major issues to consider in a risk assessment and to mitigate through risk management. However, with GDOs,

spread and persistence are their *raison d'être*, posing different legal and regulatory challenges. Moreover, GDOs will now deliberately move beyond cultivated fields, into wild populations and ecosystems. The complexity of the systems that could be affected and the impacts that could be realised increases scientific uncertainty manifold, requiring more precautionary approaches to regulation than already required with GMOs.

Working gene drives using the CRISPR/Cas[1] genome-editing platform have been recently demonstrated in several organisms in laboratory settings, only in 2015. The pairing of gene drives with CRISPR/Cas has, however, accelerated the pace of gene drive development considerably. Potentially far-reaching applications are in the pipeline, backed by huge financial investments, to which the United States' Defense Advanced Research Project Agency (DARPA) and the Bill and Melinda Gates Foundation are the biggest contributors. This means that there is real urgency in creating mechanisms to ensure that there is effective regulation of this technology in place before any release of GDOs into the environment.

It is important to set out governance and regulatory arrangements well in advance so that would-be developers are informed of the requirements they must meet. Meanwhile, time must be taken to achieve consensus among different countries as to how to apply new regulatory standards (Sustainability Council of New Zealand 2018, 7-8). The time to consider the legal and regulatory regime for gene drives and GDOs is therefore now.

While there exist biosafety regulations for research, development and use of GMOs, also termed living modified organisms (LMOs),[2] and GDOs are undisputedly covered by these laws, there is still an urgent need for specific strict regulation of these new entities, GDOs, that

[1] 'CRISPR' is short for 'clustered regularly interspaced palindromic repeats'. 'Cas' is short for 'CRISPR-associated protein'.

[2] In this paper, we generally use the term 'genetically modified organism' (GMO), unless we refer specifically to the Convention on Biological Diversity, the Cartagena Protocol on Biosafety, the Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress, or the International Plant Protection Convention, which all use the term 'living modified organism' (LMO).

goes beyond existing biosafety regulations and that must take into account their unique features and effects. The US National Academies of Sciences, Engineering, and Medicine concluded that current US regulatory practices for assessing risks or potential environmental effects of field experiments or planned releases for GMOs are inadequate for gene drives (NASEM 2016, 170-171). The change in the spectrum of organisms and environments that will be affected by the application of gene drives therefore necessitates new approaches for risk assessment and governance (Simon et al. 2018).

A regulatory regime for gene drives and GDOs must consider worst-case scenarios in order to be able to adequately deal with and to anticipate the full spectrum of possible adverse effects. While not all gene drives are global in nature, the advent of CRISPR-based gene drives, which have the potential to spread 'globally'– i.e. to all populations of the target species that are connected by gene flow – and also to be invasive in certain contexts, certainly makes this a realistic concern. Mathematical models based on empirical data show that even the least effective gene drive systems are highly invasive; release of a small number of GDOs often causes invasion into the local population, subsequently followed by the invasion of additional populations that are connected by gene flow (Noble et al. 2018). "The bottom line is that making a standard, self-propagating CRISPR-based gene drive system is likely equivalent to creating a new, highly invasive species: both will likely spread to any ecosystem in which they are viable, possibly causing ecological change" (Esvelt and Gemmell 2017, 2).

In addition, while there have been some mitigating proposals that claim to be able to restrict the spread of gene drive systems (for example, so-called 'local' or 'self-limiting' drives (Esvelt and Gemmell 2017, 4-5)), these remain largely theoretical and currently have not been demonstrated to work. Such drives are complexifiers that may also carry their own risks, due to greater difficulty in their creation and the many ecological dependencies in their function. Therefore, a legal and regulatory regime for gene drives and GDOs has to be designed to deal with the maximum implications of the technology, that is, it has to be prepared to regulate global gene drives and their potential impacts. This paper focuses largely on global gene drives and the resulting GDOs, in order to discuss their effective regulation.

BOX 1: **'Global', 'standard' and 'local' gene drives — a question of semantics**

Min et al. (2018) classify 'global' gene drives as 'standard' gene drives. These drives are likely to spread to all populations of a target species connected by gene flow. 'Local' gene drives are those that can spread to regional populations but cannot spread to all populations connected by gene flow.

These classifications are an example of the semantics at play. 'Global' gene drives of course convey the idea that such a gene drive system, once released, has the potential to spread globally, at least in so far as the target population is concerned. This is one of the major concerns and regulatory challenges raised by organisms containing gene drives. In addition, the use of the term 'global' usefully calls attention to the need for internationally agreed rules for the governance of gene drives and GDOs.

Changing the language to 'standard' gene drives, while helpfully conveying the fact that these are the prevalent gene drives that are currently being researched, detracts from the notion of potential transboundary spread globally. 'Standard' also conveys the positive idea of usual correctness or acceptability and quality. In addition, the use of the term 'standard' may provide a sense of false security, leading to an assumption that there are already some authoritative standards in place for gene drive or GDO governance, which is not the case yet.

The name 'local' gene drives, on the other hand, suggests that these types of gene drives will have limited or restricted impacts and can be confined geographically or to the immediate area of release. It should be pointed out that these various 'local' drives are at present theoretical, and it cannot be assumed *a priori* that they will work reliably, in all situations, or that they will not themselves carry their own risks.

Proposals for self-regulation by scientists, such as the development of guidance documents for best practices by those involved in research, are clearly not enough to ensure adequate oversight and governance of a technology as powerful as gene drives. An example of how self-regulation has failed with a closely related genetic technology is the recent controversy over the birth of genome-edited twins, announced in November 2018. The scientist responsible was widely condemned for conducting such an experiment without due regard for ethical or safety considerations, bringing attention to the fact that there are no international rules specifically governing this new field. The World Health Organization (WHO) later belatedly announced the establishment of a WHO Expert Advisory Committee on Developing Global Standards for Governance and Oversight of Human Genome Editing (WHO, n.d.).

While such 'rules of the road' (Adelman et al. 2017), described in some detail in this paper, can certainly play a role, and existing guidance developed for GMOs could be updated to take into account the particular characteristics of GDOs, these will have to be rooted in a legal and regulatory system that is specific and responsive to all the particular challenges raised by gene drives and GDOs. Given that GDOs have the potential to cause serious harm to the environment, a public good, it would not be appropriate to place regulation and decision-making about the technology solely in the hands of private actors (Sustainability Council of New Zealand 2018, 20). As such, a legally binding regime is needed.

Governance and regulation of gene drives and GDOs must be international in nature because of the potential for transboundary spread of GDOs. Because "ecosystems are connected in myriad ways", even a small number of GDOs introduced in one country is very likely to have ramifications well beyond its borders (Esvelt and Gemmell 2017, 5). As such, the Ad Hoc Technical Expert Group (AHTEG) on Synthetic Biology, established under the Convention on Biological Diversity (CBD), recognised that "a precautionary approach and cooperation with *all countries and stakeholders that could be affected…* might be warranted in the development and release of organisms containing engineered

gene drives, including experimental releases, in order to avoid potential significant and irreversible adverse effects to biodiversity" (AHTEG on Synthetic Biology 2017, paragraph 25, emphasis added).

The need for international governance is also recognised by the US National Academies of Sciences, Engineering, and Medicine, which called for "clearly defined global regulatory frameworks, policies, and best practice standards for implementation" (NASEM 2016, 171-172). Decisions about the application of the technology require international cooperation, which means that the establishment of an international regulatory framework for gene drives and GDOs is necessary (Norwegian Biotechnology Advisory Board 2017, 15).

At the same time, while a significant number of countries are party to the Cartagena Protocol on Biosafety and thus would likely also have national biosafety laws or regulations governing the use of GMOs or LMOs (which would apply to GDOs), these national laws and regulations are not explicit or specific to GDOs as a special category of GMOs/LMOs. National laws, however, are likely to be shaped by international developments and can be developed, or amended, if national biosafety laws already exist, to specifically take into account gene drives and GDOs. Countries may also provide for more stringent GDO regulation, as is their sovereign right, within the context of their international obligations.

This paper is concerned with the legal and regulatory aspects relevant to gene drives and GDOs, and primarily focuses on biosafety assessment and decision-making. There are many other relevant aspects as well, including the issue of 'biopiracy' and access and benefit-sharing of genetic resources, governed by the CBD's Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, which are beyond the scope of this paper.

It must be acknowledged that discussion of decision-making in the context of biosafety is often a narrower focus, and usually does not involve asking the broader, important questions which do not always fit within this framework, and which include: Who defines the problem? What are the options for solutions? Which are more sustainable, and why? Where should research and investment be directed? Who decides all this, and

how? These are fundamental issues that should rightly be addressed before embarking on activities that require biosafety assessment, rather than at the biosafety decision-making stage.

However, the reality of the situation now is that research on GDOs in the laboratory is ongoing, and deliberate releases into the environment are planned. Currently, there are no legally binding international rules and standards that are adequate to regulate these activities. This must be urgently addressed.

At the same time, legal and regulatory processes alone, while necessary, are not sufficient to confront the multiple challenges posed by gene drives and GDOs. A deep and broad global and cross-societal discussion and action on this is urgently needed. What is clear is that "this conversation should not be confined to scientists, regulators, politicians, or any single nation, no matter how strong its legislative frameworks, environmental risk management, and biosecurity networks" (Esvelt and Gemmell 2017, 5). There is urgent need to engage all citizens, especially farmers, indigenous peoples and local communities, and those who could be affected by this far-reaching technology and its impacts. This should also not just be a one-off exercise, but should rather be an ongoing feature of the approach to governance of gene drives and GDOs.

This paper will conduct a review of the international and other legal and regulatory instruments and processes that are and will be relevant to gene drives and GDOs, in so far as they address biosafety issues, and will address whether they are equipped to enforce their decisions. A particular focus will be on the CBD and its Protocols, as GDOs fall under their scope, and as they are already addressing GDOs in their substantive work. A 'Limitations' section located after each description will enumerate the problems a dependence on one or another (or even all) of the existing instruments would entail. The gaps in the existing international regime will be assessed. The specific issues raised by the characteristics of GDOs will be discussed, together with what needs to be done to address them. This paper also considers what elements are necessary in a legal and regulatory regime that is suited to the challenges posed by gene drives and GDOs, including the urgent need to take the time to remedy any serious legal and regulatory gaps *before* any release of GDOs is even contemplated.

Chapter 2

Review of Relevant International and Other Legal and Regulatory Instruments and Processes

2.1. The Convention on Biological Diversity and its Protocols

Substantial work has already taken place under the Convention on Biological Diversity (CBD) on synthetic biology and this work will continue in the coming years. The discussions on synthetic biology include the issue of 'organisms containing engineered gene drives'. At the same time, the use of terms under both the CBD and its Cartagena Protocol on Biosafety clearly defines organisms which contain engineered gene drives as living modified organisms (LMOs), the subject of the Cartagena Protocol and its Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress. Discussions under the Cartagena Protocol have begun to specifically address GDOs, via its work on risk assessment.

Additionally, another protocol to the CBD, the Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization, deals with the fair and equitable sharing of benefits arising from the utilisation of genetic resources. This treaty was negotiated to address the issue of misappropriation of genetic resources, and discussions are underway on 'digital sequence information' on genetic resources. The Nagoya Protocol may well apply to GDOs if the genetic resources (and possibly, the information related to the resources) used are sourced from provider Parties; but this paper will not discuss these issues, as our focus is on the regulations and governance needed to ensure the safety and suitability of gene drives in terms of their environmental, health and socio-economic effects.

As multilateral environmental agreements dealing with the protection of biological diversity, the CBD and its Protocols, in particular the Cartagena Protocol and the Nagoya–Kuala Lumpur Supplementary Protocol, are therefore well placed to be the main reference point in international law for GDOs.

2.1.1. Convention on Biological Diversity

Scope, objectives and key provisions

The CBD is an international, legally binding environmental treaty that was adopted at the Rio Earth Summit in 1992 and entered into force the following year. It has near-universal membership, as the United States (US) is the only non-Party country. Its objectives are the conservation of biological diversity, the sustainable use of its components and the fair and equitable sharing of benefits arising out of the utilisation of genetic resources.

As a multilateral environmental agreement, it has helped to shape global thinking and action on biological diversity. At the same time, it has fallen short of its objectives and lacks the concrete and coherent implementation and strict compliance measures that are needed to address the biodiversity crisis. Often, it is a combination of civil society action, media attention and public opinion that has played a critical role in highlighting and promoting adherence to the CBD rules and targets. Much is also dependent on national implementation and enforcement through policies and laws. Other specific limitations of the CBD are discussed later in this section.

Article 7(c) of the CBD puts in place an obligation for Parties to identify processes and categories of activities which have or are likely to have significant adverse impacts on the conservation and sustainable use of biological diversity, and to monitor their effects. It can be argued that this would include research in contained use, field trials and release of GDOs, since all these activities could result, whether unintentionally or intentionally, in impacts on biological diversity.

Article 14(a) further obliges Parties to conduct environmental impact assessments for activities that are likely to have significant impacts on

biological diversity, with a view to avoiding or minimising such effects. A release of a GDO would clearly fall under these broad obligations. For example, some gene drive systems that are designed to suppress populations can potentially cause those and related populations to go extinct. Others that spread modified characteristics through the population may result in adverse and unexpected impacts on biological diversity.

Furthermore, Articles 14(c), 14(d) and 14 (e) address the situations where activities are likely to significantly adversely affect, or pose imminent or grave danger or damage to, the biological diversity of other States. In the first instance, the responsible Parties have to meet obligations for notification, exchange of information and consultation on activities under a Party's jurisdiction or control. Immediate notification to potentially affected States and initiation of action to prevent or minimise any imminent danger or damage is also required. National arrangements are needed for emergency responses to activities or events that present a grave and imminent danger to biological diversity, supplemented by international cooperation and joint contingency plans. As the release of some GDOs can easily result in the unintentional crossing of national borders, especially when the populations concerned are spread over different countries, these provisions are thus especially relevant.

Paragraph 2 of Article 14 further obliges Parties to examine the issue of liability and redress, "including restoration and compensation", for damage that is caused to biological diversity.

The importance of Article 14 in relation to GDOs has been reiterated in several decisions on synthetic biology, in particular the most recent decision from the Conference of the Parties (COP) (see later section on 'Decision on gene drive organisms at CBD COP 14 (November 2018)').

Relevance to gene drive organisms

The specific biosafety provisions regarding "living modified organisms resulting from biotechnology" are in Articles 8(g), 19(3) and 19(4) of the CBD. A GDO is an LMO, according to the definitions under both the CBD and its Cartagena Protocol on Biosafety.

Article 8(g) refers to LMOs resulting from biotechnology that are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account possible risks to human health. Parties are required, as far as possible and as appropriate, to establish or maintain means to regulate, manage or control these risks at a national level.

Article 19(3) was the enabling provision that gave rise to the Cartagena Protocol on Biosafety, because it obliges Parties to consider the need for and modalities of a protocol in the field of the safe transfer, handling and use of LMOs.

Article 19(4) obliges Parties to provide any available information about the use and safety regulations required to handle LMOs, as well as any available information on the potential adverse impact of the specific organisms concerned, to a Party into which these LMOs are to be introduced.

Taken together, these three provisions broadly oblige Parties to establish or maintain means to regulate, manage or control risks of LMOs at a national level, to ensure safe transfer, handling and use, and to provide available information about usage, safety regulations and potential adverse impacts. The Cartagena Protocol puts into operation these obligations, which are then implemented at the national level.

For example, Parties such as the European Union and its member states have in place comprehensive biosafety legislation, requiring prior risk assessment before any LMO is deliberately released into the environment or placed on the market as food or animal feed. Biosafety laws, however, have not always proven to be effective. For example, China had to deal with a significant incident of illegal sale and planting of a genetically modified (GM) rice variety only approved for field trials and not for human consumption (Zi 2005).

Ad Hoc Technical Expert Group on Synthetic Biology

The issue of organisms containing engineered gene drives has been discussed at the CBD under the topic of 'synthetic biology'. Parties to the CBD established the AHTEG on Synthetic Biology in 2014. The 2017

report of the AHTEG discusses organisms containing engineered gene drives extensively (AHTEG on Synthetic Biology 2017). The relevant points from the report are summarised below:

(a) For some developments, such as engineered gene drives, there might be a need to consider more thoroughly the potential benefits and adverse effects at the ecosystem level. (paragraph 17)

(b) These considerations could be particularly relevant and urgent for GDOs because of the impacts they might have on biological diversity, as well as on the knowledge, innovations and practices of indigenous peoples and local communities, particularly if released into the environment. Uncertainties related to the efficacy and safety of engineered gene drive systems, as well as the relative risks that could be posed by the different applications, were noted. Additional research and guidance are needed before any GDO could be considered for release into the environment, including into lands and territories of indigenous peoples and local communities. The AHTEG noted the potential for unintended transboundary movements and geographic spread of GDOs released into the environment. "Given the current uncertainties… a precautionary approach and cooperation with all countries and stakeholders that could be affected, taking into account the need for the free, prior and informed consent of indigenous peoples and local communities, might be warranted in the development and release of GDOs, including experimental releases, in order to avoid potential significant and irreversible adverse effects to biodiversity." (paragraph 25)

(c) Updates and adaptations to LMO risk assessment methodologies might be needed to account for the lack of experience with the introduction of GDOs. (paragraph 41)

(d) Existing risk assessment considerations and methodologies might not be sufficient or adequate to assess and evaluate the risks that might arise from GDOs, due to limited experience and the complexity of the potential impacts on the environment. The development or further development of guidelines on risk assessment of GDOs would be useful. It was noted that the step

of release into the environment is irreversible and, therefore, a precautionary approach might be warranted. (paragraphs 44 and 45)

(e) Best practices for effective containment of LMOs should be adapted and applied for GDOs. It was noted that islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol, unless it is so demonstrated. Internationally agreed standards for effective containment of GDOs might be useful in order to avoid accidental releases from laboratory facilities. (paragraph 51)

The AHTEG recommendations in point (b) above are particularly relevant as GDOs may well be released in indigenous lands and territories. Research proposals that envisage future experiments with GDOs have been made for Hawaii, New Zealand, Australia and West Africa, which include areas that indigenous peoples have traditionally owned, occupied or otherwise used or acquired.

The AHTEG recommendations in point (e) above are pertinent for contained use considerations (see sections 2.4 and 4.1), especially because there are proposals to begin release of GDOs on islands, as they supposedly offer a 'confined' environment. For example, the suitability of islands in Uganda as field trial sites for gene drive mosquitoes is being investigated (Lukindu et al. 2018).

Decision on gene drive organisms at CBD COP 14 (November 2018)

At COP 14, Parties to the CBD laid down strict and precautionary conditions for any introduction of organisms containing engineered gene drives into the environment, including for experimental releases and for research and development purposes.

The CBD's Subsidiary Body on Scientific, Technical and Technological Advice (SBSTTA) had met earlier in 2018, and had reached agreement on most of its recommendations on synthetic biology, including the need to apply a precautionary approach to organisms containing engineered gene drives.

However, language asking Parties and other Governments to "refrain from" the release, including experimental release, of such organisms could not be agreed upon. Some Parties wanted a moratorium on environmental releases of organisms containing engineered gene drives, but others were opposed.

After protracted negotiations, a final compromise on the paragraph addressing organisms containing engineered gene drives was agreed upon (Decision 14/19, paragraph 11):

> Calls upon Parties and other Governments, taking into account the current uncertainties regarding engineered gene drives, to apply a precautionary approach,* in accordance with the objectives of the Convention, and also calls upon Parties and other Governments to only consider introducing organisms containing engineered gene drives into the environment, including for experimental releases and research and development purposes, when:
>
> (a) Scientifically sound case-by-case risk assessments have been carried out;
>
> (b) Risk management measures are in place to avoid or minimize potential adverse effects, as appropriate;
>
> (c) Where appropriate, the "prior and informed consent", the "free, prior and informed consent" or "approval and involvement"* of potentially affected indigenous peoples and local communities is sought or obtained, where applicable in accordance with national circumstances and legislation;
>
> [* denotes two footnotes, discussed below]

These conditions should therefore be met when Parties and other Governments are considering the release of organisms containing engineered gene drives into the environment, including for field trial and research purposes.

Both the decisions on synthetic biology and that on risk assessment and risk management under the Cartagena Protocol on Biosafety further stipulate that before GDOs are considered for release into the

environment, specific guidance may be useful, to support case-by-case risk assessment. The Parties to the Cartagena Protocol will consider, in 2020, whether additional guidance materials on risk assessment are needed for such organisms.

Therefore, it would also be prudent and responsible for Parties and other Governments to wait until such international guidance specific to the obligations in the Cartagena Protocol is available, before considering any introduction of GDOs into the environment.

Precautionary approach

In addition, a footnote to the words 'precautionary approach' recalls a series of inter-related decisions by the CBD Parties (XIII/17, XII/24 and XI/11) which set out further important principles. The decisions urged Parties and invited other Governments to take a precautionary approach to synthetic biology and to do the following, as spelt out in Decision XII/24 (paragraph 3) and summarised below:

(a) establish effective risk assessment and management procedures and/or regulatory systems to regulate environmental release, consistent with Article 3 of the Convention (which reiterates the principle in international law that States have a responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States; an issue of particular concern with GDOs, given the high potential for spread and transboundary movement);

(b) approve field trials only after appropriate risk assessments have been carried out in accordance with national, regional and/or international frameworks;

(c) carry out scientific assessments with regard to potential effects on the conservation and sustainable use of biodiversity, taking into account risks to human health and addressing also other issues such as food security and socio-economic considerations with the full participation of indigenous and local communities;

(d) encourage provision of funding for research into risk assessment methodologies and promotion of interdisciplinary research that

includes related socio-economic considerations; and

(e) cooperate in the development and/or strengthening of human resources and institutional capacities, including on methodologies for risk assessments, taking into account the needs of developing countries for financial resources, access to and transfer of technology, establishing or strengthening regulatory frameworks and for risk management.

Decision XIII/17 additionally noted that the above elements "can also apply to some living modified organisms containing gene drives" (paragraph 2).

The precautionary approach is itself to be taken "in accordance with the preamble of the Convention and with Article 14" (Decision XI/11, paragraph 4).

The preamble of the CBD notes that, "where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat". This provides Parties the right to take precautionary measures, including bans and moratoria, even in a situation where scientific knowledge is lacking.

Article 14 of the CBD meanwhile sets out principles applying to impact assessment and intended to minimise adverse effects, spelling out elements such as environmental impact assessment and allowing for public participation in such procedures; dealing with the consequences of extra-territorial impacts by promoting reciprocity, notification, exchange of information and consultation; immediate notification as well as action to prevent imminent or grave danger or damage beyond national jurisdiction; and emergency responses and international cooperation for joint contingency plans when there is a grave and imminent danger to biological diversity. Furthermore, the issue of liability and redress, including restoration and compensation for damage to biodiversity, is to be examined.

All these elements are particularly pertinent to GDOs, and are now part of the package of precautionary conditions that should apply to such

organisms, when their introduction into the environment, including for experimental releases and research and development purposes, is being considered.

"Prior and informed consent", "free, prior and informed consent" or "approval and involvement"

An additional footnote in the COP 14 decision (14/19), on "prior and informed consent", "free, prior and informed consent" or "approval and involvement", refers to the COP decision (XIII/18) that adopted the Mo'otz Kuxtal Voluntary Guidelines for the development of mechanisms, legislation or other appropriate initiatives to ensure the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of indigenous peoples and local communities when accessing their knowledge, innovations and practices, for fair and equitable sharing of benefits arising from the use of their knowledge, innovations and practices, and for reporting and preventing unlawful appropriation of traditional knowledge. These guidelines, while voluntary, set out standards for the international community on this issue.

The Voluntary Guidelines set out in detail the meanings, principles and procedural considerations of the terms (paragraph 7):

(a) *Free* implies that indigenous peoples and local communities are not pressured, intimidated, manipulated or unduly influenced and that their consent is given, without coercion;

(b) *Prior* implies seeking consent or approval sufficiently in advance of any authorization … respecting the customary decision-making processes in accordance with national legislation and time requirements of indigenous peoples and local communities;

(c) *Informed* implies that information is provided that covers relevant aspects, such as: the intended purpose … ; its duration and scope; a preliminary assessment of the likely economic, social, cultural and environmental impacts, including potential risks; personnel likely to be involved … ; procedures [that it] may entail … ;

(d) *Consent* or *approval* is the agreement of the indigenous peoples and local communities … or the competent authorities of those indigenous peoples and local communities, as appropriate, … and includes the right not to grant consent or approval;

(e) *Involvement* refers to the full and effective participation of indigenous peoples and local communities, in decision-making processes …. Consultation and full and effective participation of indigenous peoples and local communities are crucial components of a consent or approval process.

Whether "prior and informed consent", "free, prior and informed consent" or "approval and involvement" is the standard applied, depends on the national requirements of each country; it is not a menu of options to choose from. The implementation of these requirements, which is voluntary, is however subject to national rules. For example, Malaysia's Access to Biological Resources and Benefit Sharing Act requires any person intending to access traditional knowledge associated with biological resources to show evidence that the prior informed consent of the relevant indigenous and local community has been obtained. Failure to do so could result in penalties such as fines and imprisonment. The law does not specify full details of how the prior informed consent is to be obtained; therefore, the Guidelines offer useful guidance to CBD Parties in this respect.

According to the Voluntary Guidelines, these requirements should be implemented within a context of "full respect for indigenous peoples and local communities", which means "a continual process of building mutually beneficial, ongoing arrangements … , in order to build trust, good relations, mutual understanding, … and includes the full and effective participation of indigenous peoples and local communities, taking into account national legislation and customary laws, community protocols and practices of indigenous peoples and local communities…" (paragraph 8).

The grant of "prior informed consent", "free, prior and informed consent" or "approval and involvement" is temporal unless otherwise agreed. The Voluntary Guidelines also set out procedural considerations related to relevant authorities and other elements, and details on respecting

community protocols and customary law.

No similar international guidelines exist yet for obtaining the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities when considering the release of GDOs. However, since the COP 14 decision refers to the Voluntary Guidelines in relation to the differentiated levels of consent and approval required from indigenous peoples and local communities at national level, it would be prudent and responsible to only consider introducing GDOs into the environment when these details, as set out in the Voluntary Guidelines, are met.

BOX 2: **Conflicts of interest**

A conflicts of interest procedure to limit undue influence by private sector industry and other economic and vested interests on decisions in CBD fora was also adopted at COP 14 (Decision 14/33). This decision is not specific to gene drives or GDOs; however, it was adopted as a direct consequence of specific cases of conflicts of interest in relation to gene drive experts.

In 2017, a number of civil society organisations made public their findings from open records requests in the US and Canada (under the US Freedom of Information Act and the Canadian Access to Information Act), dubbing them the 'Gene Drive Files'. These findings revealed that a number of experts that had been appointed to the CBD's AHTEG on Synthetic Biology were working for institutions that received over US$100 million combined in US military and philanthropic funds, expressly to develop and test gene drive systems.

And yet, these experts were part of the expert group advising the COP's decision-making on the very same subject. These conflicts of interest had not been declared, partly because there was no requirement to do so in the CBD processes. They were only revealed because of the due diligence done by civil society.

The COP 14 decision contains a procedure for avoiding or managing conflicts of interest in technical expert groups that serve the CBD's

COP, the Cartagena Protocol's Conference of the Parties serving as the meeting of the Parties (COP-MOP), and the Nagoya Protocol on Access and Benefit Sharing's COP-MOP, or any of their subsidiary bodies. It applies to all nominated experts, regardless of who they are nominated by.

It contains, in an appendix, an 'Interest Disclosure Form', which any person nominated to serve on a technical expert group such as an AHTEG, including as Chair, would have to complete and submit to the CBD Secretariat. COP 16, to be held in 2022, may consider updates and amendments to the current procedure.

The procedure specifies that a conflict of interest "constitutes any current circumstances or interest that could lead a person to reasonably believe that an individual's objectivity in carrying out his or her duties and responsibilities for a specific expert group may be in question or that an unfair advantage may be created for any person or organization."

Each nominated expert must complete the interest disclosure form prior to the selection of experts 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."

In the interest disclosure form, various relevant financial and professional interests and activities are specified, such as employment and consulting relationships, financial investments, intellectual property and commercial interests, sources of private-sector research support, and former employment and/or other affiliation(s). In addition, relevant financial interests, of not just the individual concerned, but also their employer or the organisation nominating them, must be declared.

Apart from contact details, the contents of the interest disclosure form are publicly available upon request. This allows for the information provided or withheld by the nominated expert to be verified, thus providing some integrity to the procedure. It is also possible for any member of the public to bring relevant information that indicates a potential conflict of interest to the attention of the CBD Secretariat.

This conflict of interest procedure will help to maintain the integrity of the expert advice provided to the CBD processes. This is fundamental to good governance and is necessary in any policy and decision-making arena where technical inputs and expertise are required, such as in the case of gene drives and GDOs.

Limitations

The COP or 'Conference of the Parties' is the supreme decision-making body of the CBD, which is an international treaty that is legally binding on the countries that are Party to it. Decisions of the COP are not legally binding *per se*, in the same way that the CBD itself is binding on countries that are Party to it.

A COP decision (and a COP-MOP decision of the Cartagena Protocol and the Nagoya – Kuala Lumpur Supplementary Protocol) is a formal agreement between Parties that are signatories to a legally binding international treaty, which creates a variety of implementation obligations on those Parties. Among other things, decisions of the COP may be considered as a "subsequent agreement between the Parties regarding the interpretation of the treaty or the application of its provisions" (Vienna Convention on the Law of Treaties, Article 31.3).

The CBD only has general provisions that are applicable to GDOs, as highlighted above. There are currently no specific regulatory mechanisms to address GDOs, as specific regulation of LMOs is covered by the Cartagena Protocol on Biosafety, which was negotiated to give effect to the CBD provisions related to potential adverse impacts of LMOs resulting from biotechnology. Nevertheless, decisions of the COP further the work of the Convention, and are necessary for developing broader policy measures related to GDOs, such as its recent decision on GDOs or on issues relevant to the governance of GDOs, such as on conflicts of interest and on the free, prior and informed consent of indigenous peoples and local communities as illustrated above.

The CBD has no mechanisms for its enforcement, but a dispute settlement system between Parties in the event that there are differences in the interpretation or implementation of the CBD, and this has never been

used. At the same time, when Parties implement international treaties at the national level, domestic laws are usually enacted to do so, and these may give legal enforceability to these rules developed internationally.

Despite these weaknesses in terms of application, it is a mature environmental treaty which has been in force for more than 25 years. It has two Protocols and a Supplementary Protocol (which are legally binding international treaties linked to their parent, the CBD), subsidiary bodies and working groups and numerous work programmes. It has the buy-in of 196 countries which implement it nationally through their national biodiversity strategies and action plans.

Global peer scrutiny and public accountability, rather than the legal enforceability of the CBD, will have to continue to pressure countries to adhere to international rules. For example, the CBD decision in 2000 calling on Parties not to approve genetic use-restriction technologies (GURTs) for field testing or for commercial use (Decision V/5, paragraph 23) was a result greatly helped by a highly visible and concerted global campaign by civil society. The GURTs decision effectively resulted in a moratorium on the technology, because of the high level of public concern.

The United States is the only country in the world that is not a Party to the CBD. This is a familiar problem across numerous other international fora, and is discussed in more detail in section 3.2. GDOs are mainly being researched and developed in the US and Europe, but any COP decision on GDOs will not apply to the US as a non-Party.

Having said that, a significant number of major producer and exporter countries of GMOs are Parties to the CBD, but not the Cartagena Protocol on Biosafety. Hence, decisions of the CBD COP on these issues have a wider international reach than does the Cartagena Protocol.

2.1.2. Cartagena Protocol on Biosafety

Scope, objectives and key provisions

The Cartagena Protocol on Biosafety entered into force on 11 September 2003. As of 2019, there are 171 Parties to the Protocol. It is the first and

only international law to specifically regulate genetic engineering and GMOs. (In the Protocol, GMOs are known as living modified organisms, or LMOs.)

As a global agreement that attempts to balance the competing interests of environment and health protection and commercial and trade interests, the Protocol straddles both somewhat awkwardly. This balance is reflected in the indeterminate preambular paragraphs of the Protocol that deal with this issue, that attempt to safeguard interests on both sides:

> *Recognizing* that trade and environment agreements should be mutually supportive with a view to achieving sustainable development,
>
> *Emphasizing* that this Protocol shall not be interpreted as implying a change in the rights and obligations of a Party under any existing international agreements,
>
> *Understanding* that the above recital is not intended to subordinate this Protocol to other international agreements.

As such, the Protocol does not go far enough from the perspective of the protection of biological diversity and human health. In practice, countries implement the Protocol at the national level, working through their national interests and considerations, which may include obligations under other international agreements or fora such as the World Trade Organization (WTO). More specific limitations are discussed later in this section.

The Protocol's scope is *all* LMOs that may have adverse effects on biological diversity, "taking also into account" risks to human health (Article 4). This includes plants, food, pharmaceuticals, animals, insects, trees, LMOs for industrial use, etc. Living modified (LM) pharmaceuticals for humans are not covered by the Protocol if they are addressed by relevant international agreements made by other organisations (such as the World Health Organization, for example). The Protocol deals mainly with the transboundary movement (import and export) of LMOs, including illegal and unintentional transboundary movements.

Its objective is "to contribute to ensuring an adequate level of protection" in transferring, handling and using LMOs that may have adverse effects on biological diversity, "taking also into account" risks to human health, with a specific focus on transboundary movements (Article 1).

The language on human health is taken from the CBD. The constructive ambiguity around the language of "taking also into account risks to human health" allows some countries to argue that any risks to human health can be taken into account only if they result from an adverse effect on biological diversity. At the same time, other countries argue that any adverse effects on human health can be "taken into account" independent of adverse effects on biological diversity (Mackenzie et al. 2003, 11-12). This may lead to differences in national implementation.

For the first time in international law, there is clear recognition that LMOs are inherently different from other, naturally occurring organisms, that they may carry special risks and hazards, and therefore need to be regulated internationally. The Protocol addresses the fact that LMOs may have biodiversity and human health impacts, and that these impacts need to be risk-assessed. The Protocol also recognises that socio-economic considerations can be taken into account when making decisions on LMOs, an issue that is particularly important for developing countries.

Crucially, the Cartagena Protocol puts the Precautionary Principle into operation in decision-making, i.e., in the absence of scientific certainty, a party should err on the side of caution and could restrict or prohibit the import of LMOs on account of their potential adverse effects. In addition, the Protocol requires that Parties must consult the public when making decisions on LMOs, in accordance with their laws and regulations.

Its 'advance informed agreement' (AIA) procedure governs only the first transboundary movement between Parties of an LMO for intentional introduction into the environment. This procedure essentially operationalises the principle of prior informed consent, that exports of LMOs require the informed approval of the importing country. It also establishes the right of the importing Party to say 'no' to a given request for import.

The AIA procedure involves three key steps. First, the Party of import must be notified by the Party of export or the exporter (such as the LMO developer, which could be a biotechnology company) of the latter's intent to send LMOs. Thus, countries have an international right to be notified that an LMO is going to be shipped to them.

The Party of import then evaluates the risk assessment which has been submitted by the Party of export or exporter, or alternatively conducts its own risk assessment if it is not satisfied with the risk assessment submitted, which is usually conducted by the developer of the LMO. Precaution is also one of the general principles of risk assessment.

Finally, the Party of import makes its decision based on precaution. The decision could be for unconditional approval, approval with conditions, prohibition, a request for additional relevant information or extension of the time period for further consideration of the application. For example, in 2018, the South African authorities did not approve an application for the general release (including for planting) of a GM maize variety engineered to be drought-tolerant, insect-resistant and herbicide-tolerant (Executive Council under the GMO Act 2018). The decision was reached because the data provided by the applicant were insufficient to demonstrate the efficacy of the drought tolerance and insect resistance traits.

The AIA procedure thus places obligations on exporters to first seek the informed approval of importing Parties before the first transboundary movement for deliberate release into the environment (e.g. field trials, commercial plantings) can occur. It reverses the burden for importing Parties that usually have limited capacity and information to know what is entering into their territories and to regulate them accordingly. It also affords rights to importing Parties and places corresponding obligations on exporter countries.

In implementing this obligation, Parties either apply their domestic regulatory framework that is consistent with the Cartagena Protocol or apply the AIA procedure directly. In most cases, countries with domestic regulatory procedures would proceed in accordance with them. As such, for Parties that have national biosafety laws implementing this obligation, LMOs for deliberate release into the environment are no longer allowed

to enter their territory unless their prior informed consent is sought, a risk assessment is carried out and a decision to allow the import is given. This is the case for most of the biosafety laws in force today, although implementation and enforcement may vary.

However, the Protocol excludes some LMOs from the AIA procedure – LMOs in transit, in contained use, and those intended for food, animal feed or for processing. Nonetheless, these LMOs are still covered by the Protocol, and all other provisions of the Protocol apply to them.

LMOs that are intended for food or feed, or for processing (LMO-FFPs) are the bulk of traded LMOs. A separate procedure applies for such commodity shipments: countries that make a final decision on domestic use must notify the Biosafety Clearing-House (BCH), an online portal administered by the Secretariat of the CBD. Potential importing countries can make a decision under their domestic laws that are consistent with the objective of the Protocol, or according to the procedure in the Cartagena Protocol for LMO-FFPs. In some domestic laws, Malaysia's Biosafety Act for example, applications for approval are necessary for the import of LMOs for intentional introduction into the environment as well as for LMO-FFPs, as both types of LMOs could end up propagating in the environment, despite their intended purpose.

Parties implement their obligations under the Cartagena Protocol through national measures. In doing so, Parties interpret and apply their international obligations, often crafting comprehensive national biosafety laws and regulations dealing with all aspects of biosafety regulation, and sometimes with higher biosafety standards (see section 3.2).

Relevance to gene drive organisms

As living organisms containing engineered gene drives fulfil the criteria of (i) being a living organism; (ii) possessing a novel combination of genetic material; and (iii) resulting from the use of modern biotechnology, the Cartagena Protocol is fully applicable to them. Therefore, the Protocol's requirements pertaining to the transboundary movement, transit, handling and use of all LMOs that may have adverse effects on the conservation and sustainable use of biological diversity, including consideration of risks to human health, apply.

At the current juncture of development of GDOs, the applications are still at the laboratory research stage. It is thus also worth remembering that while LMOs destined for contained use are exempt from the AIA procedure, Parties have the right to subject all LMOs to an approvals procedure, including risk assessment, prior to decisions on import, release or even contained use. In addition, Parties have the right to set standards for contained use within their jurisdiction.

As mentioned above, Parties to the Protocol implement their international obligations through national biosafety laws and regulations. Therefore, these national biosafety rules in relation to contained use must also be examined closely (see section 3.2).

Ad Hoc Technical Expert Group on Risk Assessment and Risk Management

Article 15 deals with risk assessment and is the core business of the Cartagena Protocol, upon which decisions on import, release, etc. are made. In 2008, Parties established an AHTEG on Risk Assessment and Risk Management, and tasked it with developing further guidance on specific aspects of risk assessment and risk management.

The resulting 'Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment' comprises three parts: (i) a 'Roadmap' for risk assessment of LMOs, which explains how to conduct a risk assessment; (ii) a series of guidelines on conducting risk assessments on specific kinds of LMOs and traits – LM plants with stacked genes or traits; LM plants with tolerance to abiotic stress; LM trees; and LM mosquitoes that act as vectors of human and animal diseases; and (iii) guidance on monitoring of LMOs released into the environment.

The guidance on risk assessment of LM mosquitoes includes some general consideration of self-propagating or self-sustaining strategies that rely on gene drive systems. Elements for consideration include characterisation of the LM mosquito, unintended effects on biological diversity, vertical and horizontal gene transfer, persistence of the transgene in the ecosystem, evolutionary responses, unintentional transboundary movement, risk management strategies, and finally, containment of the

LM mosquito. However, the guidance is not focused on one particular type of technology or genetic mechanism; thus additional and more specific guidance may be necessary when conducting a risk assessment of a gene drive mosquito.

The AHTEG on Risk Assessment and Risk Management also recommended the development of additional guidance on risk assessment of LMOs developed through synthetic biology. To facilitate this, the AHTEG prepared an outline of guidance on 'Risk Assessment of LMOs developed through synthetic biology'.

The outline recognised that synthetic biology may lead to the development of LMOs containing new and significantly different features from those in the original organism or from those in nature. The potential of gene drives to alter wild populations, species and ecosystems was one consideration specific to risk assessment that was identified. The outline noted that synthetic biology tools, such as high throughput DNA sequencing and computational analyses, may make it easier to develop LMOs containing gene drive systems. It highlighted that gene drives may cause irreversible adverse effects on beneficial organisms and ecosystems and that risk assessment methodologies may need to be adapted in order to fully assess these effects.

At COP-MOP 9 in 2018, Parties adopted a decision (9/13) that establishes a new AHTEG on Risk Assessment and Risk Management (paragraph 8). It calls for broad international cooperation, knowledge sharing and capacity-building to support Parties and others in assessing the potential adverse effects of, *inter alia*, LMOs containing engineered gene drives (paragraph 5).

Importantly, specific work on LMOs containing engineered gene drives is set out as well. GDOs are the subject of a study commissioned by the CBD Executive Secretary, which would be subsequently reviewed, and analysed by the AHTEG, in order to inform the application of criteria intended to facilitate the process of identifying and prioritising specific topics that may warrant consideration for developing risk assessment guidance (paragraph 11(a) and Annex II). Parties will also consider GDOs as a topic for possible additional guidance on risk assessment at COP-MOP 10 in 2020 (paragraph 7).

Ad Hoc Technical Expert Group on Socio-economic Considerations

GDOs will clearly have socio-economic impacts, which will need to be assessed and taken into account in decision-making.

Under the Protocol, Parties have the right to take into account socio-economic considerations that arise from the impact of LMOs on biological diversity, "especially with regard to the value of biological diversity to indigenous and local communities", when taking decisions on importing LMOs (Article 26). Under national laws, socio-economic considerations or assessments may also be required as part of decision-making on GMO applications. This issue has been particularly important to developing countries, which are concerned about impacts on the livelihoods and culture of their local communities and indigenous peoples.

Under the CBD, COP 13 invited Parties to take into account socio-economic, cultural and ethical considerations when identifying the potential benefits and adverse effects of synthetic biology organisms, components and products (Decision XIII/17, paragraph 8). For example, there is concern that the use of synthetic biology to engineer microbes that can excrete compounds that mimic valuable substances, such as those found in vanilla, stevia, shea butter and silk, will threaten the market for natural products and adversely affect the livelihoods of farmers and indigenous peoples who cultivate or harvest the products (BICSBAG 2018).

COP-MOP 7 established an AHTEG on Socio-economic Considerations in 2014. In 2016, the AHTEG's composition was extended to include a representative of indigenous peoples and local communities. The outcome of its work is the 'Guidance on the Assessment of Socio-Economic Considerations in the Context of Article 26 of the Cartagena Protocol on Biosafety'. However, the AHTEG has not addressed GDOs specifically to date.

The Guidance provides principles for the assessment of socio-economic considerations and outlines the stages of the assessment process. Parties and other Governments are invited to make use of the Guidance.

The AHTEG however noted that further work was needed, in particular

on the application of methodologies and examples of application of socio-economic considerations. As decided by the Parties to the Cartagena Protocol at COP-MOP 9 in 2018, the AHTEG will continue its work to supplement the Guidance, following the collection of information and case studies via submissions from Parties and discussion in an online forum (Decision 9/14).

Decisions on unintentional transboundary movements

The issue of unintentional transboundary movements is particularly relevant to GDOs. While the central pillar of AIA in the Protocol is important for all LMOs in general, when it comes to GDOs, more attention must be paid to unintentional movements across borders. Gene drives are designed to spread genetic modifications, and the likelihood of the resulting spread of GDOs or escape from containment is high. In such cases, Article 17 of the Cartagena Protocol on 'unintentional transboundary movements and emergency measures' applies.

The provisions of Article 17 are triggered when a Party knows of a release in its jurisdiction that leads, or may lead, to an unintentional transboundary movement of an LMO that is likely to have significant adverse effects on biological diversity, taking also into account risks to human health. As soon as it knows, a Party is required to notify affected or potentially affected States, the Biosafety Clearing-House, and, where appropriate, relevant international organisations. Information that must be provided includes the estimated quantities and characteristics and/or traits of the LMO, the circumstance and estimated date of the release, the intended use of the LMO, information about the possible adverse effects on biological diversity, as well as the possibility of risks to human health, with possible risk management measures.

Incidents of unintentional transboundary movements of LMOs worldwide have occurred with alarming frequency. A total of 396 known contamination incidences and illegal releases were recorded across 63 countries between 1997 and 2013 (Price and Cotter 2014). A well-known example is that of Starlink corn, which entered the global food supply even though it had not been approved in the US (where it was grown) for food purposes, and was subject to numerous recalls (Price and Cotter 2014, 11). Another example involving a Party to the Protocol

was the unintentional export from China of rice products containing a GM variety not approved for human consumption (Zi 2005), which led to recalls in European and other countries (Price and Cotter 2014, 11). In this and similar cases, Article 17 requires the Party responsible to also immediately consult the affected or potentially affected States in order to determine appropriate responses and initiate necessary action, including emergency measures.

In the context of GDOs, the application of these obligations may soon become all too commonplace, if the rules that were put in place with more 'conventional' LMOs in mind continue to be utilised. A relevant issue to be considered is whether, for GDOs, an extended model of AIA should be considered, which can facilitate prior informed collective consent amongst *all* potentially affected parties, before any release can occur (see section 4.2).

In recent COP-MOPs, a number of decisions have been taken on Article 17, bringing its implementation forward. Among other things, COP-MOP 6 urged Parties to put in place appropriate measures to prevent unintentional transboundary movements of LMOs, and to establish a mechanism for emergency measures, in cases where significant adverse effects on biological diversity or risks to human health are likely (Decision VI/16, paragraph 1).

COP-MOP 8 adopted operational definitions of the terms 'unintentional transboundary movement' and 'illegal transboundary movement' (Decision VIII/16, paragraph 1). In Article 25 of the Protocol, Parties are required to adopt domestic measures aimed at preventing and penalising illegal transboundary movements, which are in contravention of domestic measures taken to implement the Protocol (usually national biosafety laws). Such measures, for example, could include the rejection of shipments of unapproved LMOs, such as when China rejected GM corn from the US in 2013 because that particular variety had not yet been approved in China, making it illegal (BBC News 2013).

The operational definition of unintentional transboundary movement attempts to limit the measures required under Article 17 (notification and consultation) only to situations where the LMO in question is likely to have significant adverse effects in the affected or potentially affected

States, on biological diversity, or carries risks to human health. However, the fact is that in many jurisdictions, unintentional transboundary movements are also illegal transboundary movements, and measures to prevent and penalise illegal transboundary movements would also apply to those unintentional transboundary movements, regardless of whether or not the LMO concerned is likely to have significant adverse effects on biological diversity or human health.

Network of Laboratories for the Detection and Identification of LMOs

The detection and identification of GDOs would be paramount, especially in a situation of unintentional release into the environment. Detection and identification become particularly important for GDOs in the context of liability and redress. There could, however, be challenges in obtaining the sequence information and reference materials that are necessary for countries to be able to detect and test for GDOs in their territory. Without these, regulation of unintentional and illegal transboundary movements cannot be effectively enforced. Regrettably, competent authorities are sometimes not readily provided sequence information and reference materials in such cases, and this is particularly so for LMOs in field trials. The same is likely to be true for GDOs as well.

In 2010, Parties to the Cartagena Protocol on Biosafety established the Network of Laboratories for the Detection and Identification of LMOs. The Network operates largely electronically, as a hub where experts can interact and exchange experiences on the use and development of LMO sampling and detection techniques (CBD, n.d.). The Network has developed technical tools and a draft training manual for capacity-building activities on detection and identification. It will be reviewed and finalised, and online discussions and meetings of the Network, along with capacity-building efforts, particularly for developing countries, will continue (Decision 9/11).

The AHTEG on Synthetic Biology suggested that the Network might be able to contribute to the assessment of the availability of tools for the detection of organisms developed through synthetic biology techniques, which include GDOs (AHTEG on Synthetic Biology 2017, paragraph 36). It could also assist with the identification of best practices, as well

as advising on any gaps and challenges in existing methodologies that might need to be addressed.

COP 14 of the CBD therefore requested the Executive Secretary to collaborate and convene discussions, including through the Network, for sharing experiences on the detection, identification and monitoring of organisms, components and products of synthetic biology, and to continue inviting laboratories, including analytical laboratories, to join the Network (Decision 14/19, paragraph 17(f)). The specific challenges posed by the detection and identification of GDOs need to be taken up in this work.

Limitations

The Cartagena Protocol is deficient in several respects. It was the lowest common denominator that could be agreed among big GMO exporter countries and importing countries with little capacity. Since it was negotiated with 'conventional' GMOs in mind, its deficiencies as an instrument for regulating GDOs are even more pronounced.

The major GMO-producing and exporting countries are also not Parties to the Protocol; these include the US, Canada, Australia, Argentina and Chile. However, as discussed earlier and in section 3.2, other pathways for biosafety compliance exist, and these countries and their exporters will nevertheless have to comply with the national laws of countries implementing the Protocol.

Most countries did not have national biosafety legislation or regulations prior to becoming Parties to the Protocol. When developing them, the Protocol's focus and standards were domesticated into their national laws, along with domestic regulatory issues. For countries with national biosafety laws and regulations, this is really where scrutiny is needed.

With regard to GDOs, most of the current research is taking place in the US, Australia, New Zealand and in the EU, of which the latter two are Parties to the Protocol; the Protocol's membership is not as universal as the CBD's. However, several prominent proposals for research (including field trials) and eventual deployment are in countries that are Parties to the Protocol. It is highly irresponsible for gene drive research

and deployment to take place in the absence of effective international governance, and even more so in countries that are not Parties to this Protocol.

The Protocol, as an international instrument, is largely focused on intentional transboundary movements of conventional LMOs. For the big producer and exporter countries, unimpeded trade in commodities has been their major concern. Because of this concern to allow trade in commodities to continue, the Protocol is structured around AIA and the procedure for LMOs intended for direct use as food or feed, or for processing, with provisions on unintentional and illegal transboundary movements. With GDOs, this structure is deficient, as gene drives are designed to spread genetic modifications. A single country's approval structure with inadequate provisions dealing with unintentional and illegal releases is clearly insufficient.

The Protocol's approach is centred around biosafety assessment and decision-making. Indeed, it has often been criticised as being facilitative of LMO approvals. This is a valid concern. In practice, countries are also legally bound by other international instruments that they are Party to, such as those under the WTO, which may have competing paradigms.

The Protocol, like the CBD itself, also lacks strict enforcement measures. Its provisions on compliance are largely facilitative and focus on cooperation, advice and assistance, unlike the WTO's dispute settlement mechanism for example, which entails trade sanctions and other censures.

Furthermore, under the Protocol, socio-economic issues are merely *considerations* that countries may take into account, or not, in their decision-making. Socio-economic issues are treated as conceptually separate from risk assessment. With GDOs, these issues and their assessment are arguably even more pressing than they have been with LMOs. Enlarging the space to address the broader questions such as problem formulation, alternative solutions, research and technology choices and power relations in respect to decision-making structures, is also a major challenge that needs to be addressed.

2.1.3. Nagoya – Kuala Lumpur Supplementary Protocol on Liability and Redress

BOX 3: **Liability and redress**

Liability is an obligation of a (natural or legal) person to provide compensation or take redress measures for damage resulting from an action or a situation for which that person is responsible. Liability arises when it is established in fact and in law that there has been damage caused. It must further be established that there is an identifiable person who is responsible. At that point, the issue of compensating for or redressing the harm done can be dealt with (Nijar 2007).

The purpose of liability rules can be four-fold: (i) they have a preventive function, in that they provide incentives for the implementation of and compliance with existing rules; (ii) they include an absorptive function, by internalising the environmental, health, socio-economic and other costs of an activity; (iii) they also have a punitive function, as they impose sanctions against wrongful conduct and help implement the 'Polluter Pays' principle; and (iv) they exert a corrective function, that requires the restoration of the damage (Secretariat of the Convention on Biological Diversity 2011).

Scope, objectives and key provisions

The Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress to the Cartagena Protocol on Biosafety is a separate treaty that deals specifically with the issue of liability and redress for damage resulting from the transboundary movements of LMOs. It entered into force in March 2018, and there are currently 44 Parties.

As an international law only newly in force, it is expected that more countries will become Parties. However, this may be a slow process, given that some countries still do not have their national biosafety systems in place, much less any liability and redress rules for LMOs. It is also probable that not as many countries as are Parties to the Cartagena Protocol will become Parties to the Supplementary Protocol, as the political landscape has shifted, 16 years after the entry into force of the Cartagena Protocol. Developing countries, who were the strong

proponents for international liability and redress rules, are now more involved in experimenting with, planting and commercialising LMOs. The application of these liability rules to real situations of damage arising from LMOs has not yet been tested, so it remains to be seen how effective the Supplementary Protocol will be.

The Supplementary Protocol's objective is "to contribute to the conservation and sustainable use of biological diversity, taking also into account risks to human health, by providing international rules and procedures in the field of liability and redress relating to living modified organisms" (Article 1). This mirrors the objectives and the language of the Cartagena Protocol.

The Supplementary Protocol requires Parties to provide at the national level for rules and procedures that address damage from LMOs where such damage falls under the definition set out in its Article 2. As discussed earlier, under the Cartagena Protocol and hence also under the Supplementary Protocol, GDOs clearly fall within the definition of LMOs.

Damage is defined in the Supplementary Protocol as an adverse effect on the conservation and sustainable use of biological diversity, and also takes into account risks to human health. This means that damage is not restricted to damage to biological diversity alone; damage to human health is also considered. Like with the Cartagena Protocol, there is ambiguity about exactly how to interpret this inclusion of human health; this is left to Parties to implement at national level.

The Supplementary Protocol applies to damage resulting from LMOs that find their origin in a transboundary movement (Article 3). The LMOs referred to are those (i) intended for direct use as food, feed or for processing; (ii) destined for contained use; and (iii) intended for intentional introduction into the environment. It also applies to damage resulting from unintentional transboundary movements and illegal transboundary movements.

Furthermore, domestic law implementing the Supplementary Protocol shall also apply to damage resulting from transboundary movements of LMOs from non-Parties. This means that Parties are obliged in their

domestic laws to ensure that all transboundary movements of LMOs, even from non-Parties, are addressed. This is an important issue, as some of the major producers and developers of LMOs, such as the United States and Argentina, are non-Parties to the Cartagena Protocol and hence are also not Parties to the Supplementary Protocol. In practice, Parties' national biosafety laws would apply to transboundary movements of LMOs regardless of whether the LMOs originate from countries that are Parties to the Protocol or not. The Supplementary Protocol simply makes this mandatory and explicit. However, if there is transboundary movement between two non-Parties, the Supplementary Protocol will not apply, only the two countries' domestic liability rules.

The central obligation that Parties to the Supplementary Protocol assume is to provide for response measures in the event of damage, or a sufficient likelihood of damage, resulting from LMOs (Article 5).

It must be pointed out that the Supplementary Protocol takes an 'administrative approach', whereby liability would be a matter to be resolved between the liable entity and the executive arm of a government, and response measures are required of the operator (person or entity in control of the LMO) or the competent authority (the national entity responsible, usually an environment agency), if the operator is unable to take response measures.

The operator is defined as any person in direct or indirect control of the LMO, and could include the permit holder, person who placed the LMO on the market, developer, producer, notifier, exporter, importer, carrier or supplier. This is determined by domestic law.

Response measures are defined as reasonable actions to (i) prevent, minimise, contain, mitigate or otherwise avoid damage, as appropriate; and (ii) restore biological diversity. Measures must be implemented by, and in accordance with, domestic law. Response measures are required in both situations where damage to biodiversity has already occurred, and when there is a sufficient likelihood that damage will result if timely response measures are not taken.

It is understood that the operator is responsible for paying for the costs incurred in the exercise of its obligations under the Supplementary

Protocol. In addition, the competent authority has the right to recover from the operator the cost and expenses of, and incidental to, the evaluation of the damage and the implementation of response measures. In terms of damage to biological diversity and the response measures required, the costs could be enormous. The Supplementary Protocol does not provide for financial guarantees, in case the operator does not or cannot pay. It merely acknowledges the right of countries to require financial security in their national laws. As with many of these agreements, the Supplementary Protocol lacks an enforcement mechanism.

Relevance to gene drive organisms

As discussed earlier, under the Cartagena Protocol and hence also under the Supplementary Protocol, GDOs clearly fall within the definition of LMOs.

In relation to GDOs, impacts on the environment and biological diversity, human and animal health, and on socio-economic conditions are likely to be greater than with 'conventional' GMOs. High-risk technologies demand high levels of responsibility and accountability. The irreversible nature of their impact and possible wide geographic spread once released mean that there is high potential for serious harm. The likelihood of unintentional and illegal transboundary movement is high.

A strict and legally binding international liability regime that is effective against the significant risks that GDOs pose is therefore essential. However, the Supplementary Protocol falls far short of what was envisaged when developing countries called for its negotiation. Instead of the international instrument that would help to ensure the responsibility and accountability of the producers and exporters of LMOs, the threshold for establishing damage is high, and much of the burden has been shifted to the recipient countries themselves, without the advantage of the necessary financial guarantees. In the case of GDOs, these deficiencies are further amplified.

The Supplementary Protocol applies to damage from LMOs and GDOs that find their origin in a transboundary movement. With GDOs currently being researched and developed, this may not always be the case. Not all GDOs may be imported or exported; they may be intended

for domestic use only, but may still cause significant damage. However, the Supplementary Protocol also applies to damage resulting from unintentional transboundary movements and illegal transboundary movements, which is particularly relevant to GDOs.

Limitations

The Supplementary Protocol is newly in force but it currently has limited participation, with only 44 Parties. This means that few countries have the necessary domestic rules to implement the Supplementary Protocol and for liability and redress for LMOs/GDOs.

The central approach of the Supplementary Protocol is an administrative approach, which may not be adequate to deal with the damage caused by LMOs and GDOs in particular (see Box 4). Civil liability approaches, whereby victims of damage can turn to national courts for redress and enforcement of judgments, that are specific to LMOs and GDOs are not required, just permitted, and Parties' rights to put in place domestic civil liability rules and procedures are preserved under the Supplementary Protocol. The first review of the Supplementary Protocol, five years after entry into force (in 2023), will include a review of the effectiveness of the provision of civil liability.

The standard of liability that Parties should apply for domestic civil liability rules is left to national legislation. The Supplementary Protocol does not require Parties to apply a strict liability standard for civil liability rules on LMOs, which is a limitation (see Box 5).

Besides the issue of rules and procedures on civil liability, much of substance in the Supplementary Protocol is also left to national legislation. These include: defining the 'operator'; criteria to address damage that occurs within national jurisdiction; the application of damage from import of LMOs from non-Parties; establishing the causal link between the LMO and the damage; exemptions or mitigations; time limits; financial limits; and the provision of financial security.

In addition, the most important element of the Supplementary Protocol is qualified by reference to domestic laws – response measures are to be implemented "in accordance with domestic law" (Article 5.8).

BOX 4: **Administrative approach, not civil liability**

During the negotiations for the Supplementary Protocol, most developing countries had wanted a binding international regime that would set substantive rules on civil liability, whereby victims of damage from LMOs can turn to national courts for redress and enforcement of judgments.

However, due to the compromises made during the negotiations, the Supplementary Protocol takes an 'administrative approach', whereby liability would be a matter to be resolved between the liable entity and the executive arm of a government. 'Response measures' are required of the operator (person or entity in control of the LMO) or the competent authority (government agency), that is, if the operator is unable to take response measures. This is the approach taken in the EU Environmental Liability Directive, for example. It is however a novelty for an international environmental liability regime and it remains to be seen how it will work at the international level with the subject matter of LMOs.

The administrative approach of the Supplementary Protocol does however in effect employ a strict liability approach (see Box 5). When there is damage or sufficient likelihood of damage, then response measures should be implemented. Of course, a causal link needs to be established between the damage and the LMO in question.

Under the Supplementary Protocol, it is not necessary to establish the fault of the operator. The action or inaction of the operator is not the trigger for establishing liability and providing for response measures. Damage, or the sufficient likelihood of damage, is what triggers the response measures that need to be taken.

In addition, the administrative approach itself theoretically allows for preventive action to "prevent, minimize, contain, mitigate, or otherwise avoid damage". It could also facilitate a speedier response in terms of restoring biological diversity, without having to go through a judicial process.

Reference: Nijar 2013.

BOX 5: **Strict liability is the necessary civil liability standard for GDOs**

In common law jurisdictions, under a *fault-based liability regime*, it is necessary to establish that a person has a duty of care towards the victim, that there has been a breach of that duty, and that the breach of that duty has caused the damage. Multiple difficulties can arise with this, especially in the case of GMOs and GDOs. The burden of proof lies with the victim who has suffered the damage to show evidence of each element.

With *strict liability,* it is sufficient that the damage is proven and a causal link between the damage and the GMO/GDO is shown, which means that liability is established without proof of fault. The burden of proof is reversed, and instead the person responsible is required to show that its GMOs/GDOs are safe when there is damage. Defences are available and can be legally applied. Strict liability is commonly the standard for product liability, for example.

This is aligned with the biosafety approvals procedure, where the operator seeks regulatory approval by demonstrating through risk assessment that the LMO is 'safe'. The regulator applies the Precautionary Principle, and makes a decision.

It has been argued that the application of the Precautionary Principle and strict liability go hand in hand. The Precautionary Principle requires action to avoid or minimise risks, even in the face of scientific uncertainty, and full scientific certainty is not necessary for taking preventive or precautionary action. Strict liability assigns liability so long as causation between the GDO and the damage can be established. It dispenses with the need for establishing the breach of the duty of care of the responsible person.

In the case of GDOs, the risks are inherent to their nature and construction. For strict liability, the focus is on the actual performance and condition of the GDO. For fault-based liability, the focus is on the care taken by the responsible person. As such, strict liability is the necessary standard of liability for GDOs.

For activities involving ultra-hazardous risks especially, strict liability is already evolving to become customary international law. It has been argued that these risks include most of the serious risks arising from many other modern technologies, including activities which may cause a substantial change in the natural environment, significant pollution and the modification of biological processes. It is also the standard of liability in several international treaties dealing with environmental harm from hazards ranging from nuclear activities to oil pollution.

References: Nijar 2000; 2007.

In contrast to a legally binding international civil liability regime, which was what most developing countries had wanted, the administrative approach of the Supplementary Protocol places a large burden for addressing damage on national authorities.

The competent authority, which is the government agency responsible and could include a dedicated biosafety agency or a department of environment, has to identify the operator, evaluate the damage and determine which response measures should be undertaken. If the operator fails to implement appropriate response measures, the competent authority may do so. Although the competent authority may recover costs and expenses from the operator, substantial resources and capacity are still required, which most developing countries may not have.

Despite this, financial security, in terms of insurance or other means of guaranteeing redress, is not required under the Supplementary Protocol. Parties only retain their right to provide for financial security in their domestic laws. Even so, this right is qualified by reference to consistency with rights and obligations under international law, taking into account the careful balance struck in the Cartagena Protocol's preamble on the mutual supportiveness of trade and environment agreements. Compulsory insurance or other financial guarantees, as well as a supplementary compensation fund, are necessary, at a minimum, for GDOs.

However, in accordance with the provision on financial security in the Supplementary Protocol (Article 10), the first meeting of the Parties to the Supplementary Protocol in 2018 requested the Secretariat to undertake a comprehensive study on financial security for consideration at its next meeting in 2020. The first review of the Supplementary Protocol, five years after entry into force (in 2023), will also include a review of the effectiveness of the provision on financial security.

Furthermore, the Decision adopted at COP-MOP 5 on liability and redress states that where the costs of response measures have not been covered, such a situation may be addressed by additional and supplementary compensation measures. These may include arrangements to be addressed by the COP-MOP in the future.

These opportunities must be taken and seriously addressed as part of the mandated future work of the Supplementary Protocol, given the urgency and gravity of the potential damage from GDOs.

Another considerable hurdle in the Supplementary Protocol is that response measures are to be taken only if damage is measurable or otherwise observable, and must take into account, wherever available, "scientifically-established baselines recognized by a competent authority that takes into account any other human induced variation and natural variation" (Article 2.2(b)). Damage must also be "significant", for which determination is specified by the Supplementary Protocol (Article 2.3). Only once a threshold of significant, measurable or observable damage has been met, that takes into account scientifically established baselines, does the requirement to take response measures arise. This is particularly challenging in the context of GDOs.

2.2. Other international agreements and standards of relevance to gene drive organisms

This section will address some of the other international agreements and standards of more relevance to GDOs currently. The agreements and standards discussed here cover areas of specific governance of GDOs. These include the WTO's Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) and two of the

international standard-setting bodies that are explicitly recognised by the SPS Agreement – the International Plant Protection Convention and the World Organisation for Animal Health.

The other international standard-setting body recognised by the SPS Agreement, the Codex Alimentarius Commission, is not addressed in this section. This is primarily because Codex provides for the international regulation of food safety, and gene drive applications are not envisaged yet for food crops. This fact is also a matter of technical challenge, as current CRISPR-based gene drives cannot be easily developed in plants. However, there may be future applications that affect food safety, for example if gene drives are successfully used to make weeds such as pigweed susceptible to herbicides; if such modifications spread to related amaranth species used for food in some countries, there could be unanticipated effects (NASEM 2016, 76), including on food safety. Gene drives could also theoretically be used as a tool for genome editing in livestock breeding (Gonen et al. 2017), resulting in gene drive animals potentially entering the food supply. These applications are pretty far in the future, although should any come to fruition and raise potential international food safety issues, then the Codex would become relevant.

The other agreements and standards that are reviewed in this section are those that are relevant to the potential hostile use of gene drives, given the 'dual use' nature of the technology. We also examine the UN Declaration on the Rights of Indigenous Peoples, which sets international norms on the rights of indigenous peoples, who could be affected by any release of GDOs, and on whom the CBD and its Protocols place particular importance, given their role as custodians of biological diversity.

None of the agreements or standards reviewed in this section has a biosafety impetus as its starting point. In particular, the SPS Agreement operates within a trade liberalisation context. (The uneasy relationship between trade and environment is discussed in section 2.1.2, in so far as it plays out between the WTO and the Cartagena Protocol on Biosafety.) It sets out the permissible measures for WTO members on sanitary and phytosanitary action without falling foul of its international rules for advancing free trade.

2.2.1. Agreement on the Application of Sanitary and Phytosanitary Measures

Scope, objectives and key provisions

The Agreement on the Application of Sanitary and Phytosanitary Measures (SPS Agreement) is one of the WTO's agreements that were signed in 1994. WTO agreements are legally binding on WTO members, and the WTO is the only international organisation with a *formal and enforceable dispute settlement system*, giving it considerable legal force. In a dispute, a sanction of last resort could be the raising of duties on imports from the losing party, providing a strong incentive for members to comply with WTO dispute panel rulings. As of July 2016, there are 164 WTO members.

The SPS Agreement deals with sanitary and phytosanitary measures that "may, directly or indirectly, affect international trade" (Article 1.1). These measures include laws, regulations, requirements, procedures and decrees. A WTO member intending to apply measures to restrict trade for the protection of the life or health of humans, animals or plants has to comply with the SPS Agreement.

Annex A of the SPS Agreement defines a sanitary or phytosanitary measure as any measure applied to: (i) protect animal or plant life or health from risks arising from the entry, establishment or spread of pests, disease, disease-carrying organisms, or disease-causing organisms; (ii) protect human or animal life or health from risks arising from additives, contaminants, toxins, or disease-causing organisms in foods, beverages or feedstuffs; (iii) protect human life or health from risks arising from diseases carried by animals, plants or products thereof, or from the entry, establishment or spread of pests; or (iv) prevent or limit other damage from the entry, establishment or spread of pests.

WTO members are allowed to set their own standards, as long as the measures are applied only to the extent necessary to protect human, animal and plant life or health; are based on scientific principles and maintained with sufficient scientific evidence; are not a disguised trade restriction; do not arbitrarily or unjustifiably discriminate between members where identical or similar conditions prevail; and are not

more trade-restrictive than required to achieve an appropriate level of protection (Chee and Lim 2007, 430).

WTO members are encouraged to use international standards, guidelines and recommendations where these exist, although they may use measures that result in higher levels of protection if there is scientific justification (i.e. they have conducted an evaluation of available scientific information and have decided that the international standards are not sufficient to achieve their appropriate level of protection). Alternatively, there needs to have been a risk assessment conducted according to the SPS Agreement provisions as a basis for a sanitary or phytosanitary measure taken (Chee and Lim 2007, 430).

In general, while the SPS Agreement allows WTO members to restrict trade on the basis of sanitary and phytosanitary measures, the logic and rationale of free trade prevail. In effect, this means that any measures applied are the minimum necessary to protect human, animal and plant life or health.

BOX 6: **Existing application of the SPS Agreement to GMOs**

The application of the SPS Agreement to GMOs has been confirmed by the disputes brought in 2003 by the United States, Canada and Argentina against the European Union: *European Communities – Measures Affecting the Approval and Marketing of Biotech Products.*

The dispute settlement panel concluded that the European Communities (EC) applied a general *de facto* moratorium on approvals of biotech products, which was in effect on the date of panel establishment, i.e., August 2003. However, the moratorium itself was not an SPS measure as it was not applied for achieving the EC level of sanitary or phytosanitary protection. The decision to apply a general moratorium, however, was deemed a procedural decision to delay final substantive approval decisions. The EC was thus found to have acted inconsistently with its obligations in that it did not ensure that procedures are undertaken and completed without 'undue delay'.

The issue of undue delay is relevant, as the SPS Agreement also covers the operation of sanitary and phytosanitary measures, and these operational measures include undue delays in a sanitary-or phytosanitary-related approval process.

Similarly, the EC failure to consider for final approval applications concerning certain specified biotech products resulted in undue delay in the undertaking and completion of the approval procedures with respect to 24 of 27 biotech products.

The national marketing and import bans in some European countries on specific products already approved at Community level (so-called safeguard measures) were also subject to dispute. The panel found that the safeguard measures were not based on a 'risk assessment' as required by the SPS Agreement, and hence were inconsistent with requirements that SPS measures are based on scientific principles and not maintained without sufficient scientific evidence. The panel also found that there was sufficient scientific evidence for a 'risk assessment', thus the safeguard measures were inconsistent with the SPS clause that allows provisional measures only where "relevant scientific evidence is insufficient" (Article 5.7).

Reference: WTO 2017a, 120.

Relevance to gene drive organisms

It is likely that the SPS Agreement will apply to GDOs that enter international trade and that pose risks to animal or plant life or human health arising from the entry, establishment or spread of pests, diseases, disease-carrying organisms or disease-causing organisms. As yet, there are no such commercially traded GDOs, but this may be the case in the future.

If this is the case, measures taken by WTO members to address the risks of GDOs that are imported or exported would count as sanitary and phytosanitary measures and would have to comply with the requirements of the SPS Agreement. Such measures, which can also be biosafety measures, may include pre-marketing approval procedures, monitoring obligations, restrictions and conditions, and bans or moratoria.

Limitations

The rationale of the SPS Agreement, while allowing for sanitary and phytosanitary measures, is one that rests on ensuring that free trade can continue and that there is no disguised protectionism. WTO members, while balancing their biosafety interest, would need to navigate their biosafety measures related to GDOs in international trade carefully, if they are also sanitary and phytosanitary measures under the SPS Agreement.

Issues of undue delay and risk assessment, including whether or not temporary bans can be applied, can be expected to remain challenging. As seen in the EC case (Box 6), procedural delays may fall foul of the SPS Agreement, while meeting its risk assessment requirements may be difficult. Moreover, recourse to Article 5.7, that is, the ability to apply provisional measures where scientific information is insufficient, is not that straightforward, as discussed below.

Articles 2 and 5.1 of the SPS Agreement stipulate that, while members have the right to take sanitary and phytosanitary measures necessary for the protection of human, animal or plant life or health, such measures have to be applied only to the extent necessary, based on scientific principles, and supported by scientific evidence. The measures must therefore be based on a scientific risk assessment.

In practice, the SPS Agreement provides a privileged role to scientific evidence in determining the proper scope of risk regulation (Peel 2004). This has resulted in a move away from broader and more holistic views of risk assessment (see, for example, arguments by Wickson and Wynne 2012), to one that merely evaluates risk based on 'sound science'. As a result, while the SPS Agreement preserves a member's right to determine an acceptable level of risk, levels that may be motivated by domestic social considerations or other legitimate policy concerns, these will tend to be marginalised by this approach, which overtly links the justification for SPS measures to the scientific evidence of risk (Peel 2004).

In relation to GDOs, the question is whether such privileging of scientific evidence compromises our ability to thoroughly assess their implications. Where, for instance, the risk identified on the basis of scientific evidence

suggests the risk is negligible or very low, any implementation of stringent risk management measures will appear 'disproportionate' and likely WTO-incompatible, even though such measures may be justified if a more broadly oriented assessment had been conducted (Peel 2004), such as one that includes socio-economic considerations or acknowledges scientific uncertainty (Wickson and Wynne 2012).

Any biosafety measure will be questioned as to whether it is the least trade-restrictive measure. Article 5.6 of the SPS Agreement states that measures should be "not more trade restrictive than required to achieve their appropriate level of sanitary or phytosanitary protection". A measure is deemed not more trade-restrictive than required, unless there is another measure reasonably available that achieves the appropriate level of sanitary or phytosanitary protection, and is significantly less restrictive to trade.

While this might make sense from a trade perspective (i.e. ensuring that SPS measures still allow trade to continue), from the point of view of biosafety this is not necessarily fully protective of health and the environment. This could be especially so if there are scientific uncertainties or long time lags in the manifestation of risks (or in the collection of data or evidence), which are all valid scientific issues, as might well be the case with GDOs.

The SPS Agreement, in its Article 5.7, allows for temporary bans if they are provisional. Where scientific evidence is insufficient, provisional measures may be taken on the basis of available pertinent information, provided additional information is subsequently sought for a "more objective assessment of risk" and the measures are reviewed "within a reasonable time". These requirements – that there is insufficient scientific evidence, that there is some information on which to justify the measure, that there is continued seeking of additional information, and that the measures are periodically reviewed – have been judged to be cumulative in nature and equally important.[3] Whenever one of these requirements is not met, the measure concerned is inconsistent with Article 5.7.

[3] As determined by the Panel in *Japan – Measures Affecting Agricultural Products* and upheld by the Appellate Body (WTO 2017b, 37).

Thus, in order to justify maintaining a provisional measure, all the requirements have to be met and continuously demonstrated, placing significant obligations and regulatory burdens on the authorities concerned. Moreover, the measures are only provisional and temporary, excluding more permanent moves that may be necessary in order to be fully protective of health and the environment.

It is likely that the SPS Agreement would offer limited protection from the risks of GDOs, as its imperative is to circumscribe sanitary and phytosanitary protection in the interest of free trade.

2.2.2. International Plant Protection Convention

Scope, objectives and key provisions

The International Plant Protection Convention (IPPC) is an international, legally binding treaty that sets international phytosanitary standards for plants. It has 183 contracting parties (as of September 2018) and the secretariat is hosted by the UN Food and Agriculture Organization (FAO).

The IPPC aims to protect wild and cultivated plants by preventing the introduction and spread of pests of plants and plant products, and by promoting appropriate measures for their control. The treaty is essentially a framework and a forum for international cooperation, harmonisation and technical exchange between its contracting parties. Its implementation involves collaboration by National Plant Protection Organizations (NPPOs), which are established by governments for the purposes of the IPPC, and Regional Plant Protection Organizations (RPPOs), which are regional coordinating bodies.

NPPOs are usually existing agencies with the mandate to address plant phytosanitary issues. For example, the US has its Animal and Plant Health Inspection Service – Plant Protection and Quarantine (APHIS – PPQ), and in Malaysia there is the Crop Protection and Plant Quarantine Division of the Department of Agriculture. An RPPO is an intergovernmental organisation functioning as a coordinating body for NPPOs at regional level; for example, all members of the Pacific Community are members of the Pacific Plant Protection Organisation.

Such RPPOs provide advice on phytosanitary measures, for example, by issuing an 'Alert List' as early warning of certain pests that could be potential risks,[4] or to highlight possible candidates for a Pest Risk Analysis.

While the IPPC itself is legally binding, the standards developed and adopted under it are not. However, the standards are explicitly recognised by the SPS Agreement as international standards for plant health. Phytosanitary measures that conform to IPPC standards are deemed necessary to protect plant life or health and are presumed WTO-consistent, potentially shielding WTO members that conform to such standards from challenge at the WTO. This provides an incentive for WTO members to ensure that their phytosanitary measures conform to IPPC standards.

International standards for phytosanitary measures (ISPMs) are developed through the work programme of the Commission on Phytosanitary Measures. Non-contracting parties to the IPPC are encouraged to observe these standards.

BOX 7: **Existing application of the IPPC to GMOs**

In April 2004, the Interim Commission on Phytosanitary Measures endorsed a supplement on pest risk analysis for LMOs, resulting in an integrated standard: ISPM No. 11 'Pest risk analysis for quarantine pests including analysis of environmental risks and living modified organisms'. It includes guidance on evaluating potential phytosanitary risks to plants and plant products posed by LMOs.

ISPM No. 11 harmonises and standardises the way countries analyse risks that LMOs may pose to plant health. A country may use the standard to determine which LMOs pose a threat and if necessary can prohibit or restrict their import and domestic use. The standard is not just restricted to genetically modified (GM) plants, but also covers other LMOs that may be harmful to plants, such as GM insects, fungi and bacteria. Direct and indirect effects on plants or plant products are both considered.

[4] See an example from the European and Mediterranean Plant Protection Organization: https://www.eppo.int/ACTIVITIES/plant_quarantine/alert_list

The standard includes the assessment of the risks of LMOs to plants, in so far as they are pests of plants (e.g. if a GM plant subsequently becomes a weed or if a GM insect becomes a pest). Phytosanitary risks may result from certain traits introduced into the organism, such as those that increase the potential for establishment and spread, or from inserted gene sequences that do not alter pest characteristics but that might have unintended consequences.

Once an LMO is determined to be a potential pest, it goes through a pest risk assessment process, involving three steps: (i) pest categorisation; (ii) assessment of the probability of introduction and spread, including an analysis of both intentional and unintentional pathways of introduction and intended use. The probability of gene flow and gene transfer should be considered, as should the probability of expression and establishment of that trait, while the survival capacity without human intervention of the LMO should also be assessed; and (iii) assessment of potential economic consequences (including environmental impacts).

The conclusions from the pest risk assessment are then used to decide whether pest risk management measures should be taken. If no satisfactory measure is available to reduce risk to an acceptable level, the final option may be to prohibit importation of the relevant commodities. This is viewed as a measure of last resort. Nonetheless, the implementation of phytosanitary measures is not considered permanent, and should be monitored, reviewed and modified if necessary.

Relevance to gene drive organisms

The standards set by the IPPC have been identified to be possibly relevant to the components, organisms and products resulting from synthetic biology (Secretariat of the Convention on Biological Diversity 2015, 96-97). This would include GDOs. In particular, ISPM No. 11, as discussed in Box 7, is directly relevant.

Annex 3 of ISPM No. 11 identifies the potential phytosanitary risks from LMOs. Those relevant to GDOs include: changes in adaptive characteristics, which may increase the potential for introduction or

spread, such as alterations in dispersal ability of pests; adverse effects of gene flow or gene transfer, such as the potential to overcome existing reproductive and recombination barriers which could result in pest risks; and adverse effects on non-target organisms, such as changes in host range, including cases where the LMO is used as a biological control agent or organism otherwise claimed to be beneficial.

These examples could reasonably be risks some GDOs are expected to pose, particularly given their potential for spread, both intended and otherwise. Currently, several agricultural insect pests are the targets of gene drive research, and a prominent example is work on the spotted wing fruit fly, which is a pest of soft fruit (Buchman et al. 2018). While the modifications are aimed at population suppression, any unintended effects that might, for example, change the characteristics of the pests would have to be evaluated according to ISPM No. 11.

The analysis of unintentional pathways of introduction included in the pest risk assessment process is also particularly significant, given the high potential for unintentional dissemination of GDOs.

Limitations

The IPPC standard on LMOs would only apply to GDOs that enter international trade and are deemed to be plant pest risks. The determination of whether a GDO is a potential plant pest would be the crucial first step in order to conduct the pest risk analysis.

However, the application of the standard to GDOs that are not imported and exported or that do not disrupt international trade is currently limited, with the exception of the possibility of identifying unintentional pathways of introduction.

For WTO members, as the IPPC is essentially the implementation of the SPS Agreement applied to plant pest risks, the risk management measures that are recommended under ISPM No. 11 have to be non-discriminatory and least trade-restrictive. This means that any measures taken have to be the minimum necessary to protect plant health, while ensuring that trade can continue as unimpeded as possible. This may not provide for adequate protection from the risks of GDOs.

2.2.3. World Organisation for Animal Health standards

Scope, objectives and key provisions

In 1924, the international agreement that led to the creation of the Office International des Epizooties (OIE) was signed. In 2003, the OIE became the World Organisation for Animal Health, but kept its historical abbreviation. It is an intergovernmental organisation responsible for improving animal health worldwide, and, as of 2018, has 182 member countries.

The OIE is recognised by the SPS Agreement as the international organisation responsible for standard-setting regarding animal health. Within this mandate, it publishes health standards for international trade in animals and animal products. Phytosanitary measures that conform to OIE standards are deemed necessary to protect animal life or health and are presumed WTO-consistent, potentially shielding WTO members that conform to such standards from challenge at the WTO. This provides an incentive for WTO members to ensure that their phytosanitary measures conform to OIE standards.

The OIE publishes two codes and two manuals (Terrestrial and Aquatic), as the principal references for WTO members. The Terrestrial Animal Health Code and Aquatic Animal Health Code respectively are intended to ensure the sanitary safety of international trade in terrestrial animals and aquatic animals and their products. The codes traditionally addressed animal health and zoonoses, but in recent years have covered issues such as animal welfare.

BOX 8: **Existing application of the OIE standards to GMOs**

In May 2005, OIE members adopted a Resolution on 'Applications of Genetic Engineering for Livestock and Biotechnology', which requested the constitution of an Ad Hoc Group on Biotechnology to support the development of harmonised technical standards for the regulation of biotechnology-derived animal health products, and GM production animals.

Members also asked the OIE to prioritise the development and adoption of standards, recommendations and guidelines for:

- research on the use of live attenuated vaccines in animal health
- use of DNA vaccines
- animal health risks linked to cloning
- assessing the health of embryos and production animals derived from cloning, and associated safety of cloned production animals and their products
- exclusion of unapproved animals and products from the livestock population and segregation from the feed and food supply
- identification, testing, and certification for international trade in animals and their products for which biotechnology procedures have been employed.

Relevance to gene drive organisms

Should animal GDOs or GDOs used to control animal diseases be imported or exported, the standards set up by the OIE would be relevant to them. For example, gene drive research is being carried out on Australian sheep blowflies, which cause 'blowfly strike', resulting in lesions in infested areas of the sheep's skin, thus affecting animal welfare and productivity.

Limitations

To our knowledge, there has been no work done yet at the OIE on GDOs. The OIE standards would only apply to animal GDOs or GDOs used to control animal diseases in international trade. As such, the standards would have limited relevance to GDOs currently.

2.2.4. Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction

Scope, objectives and key provisions

The Convention on the Prohibition of the Development, Production and Stockpiling of Bacteriological (Biological) and Toxin Weapons and on their Destruction, also known as the Biological Weapons Convention (BWC), entered into force in 1975. There are currently 182 State Parties who are legally bound by this treaty.

The BWC was the first multilateral disarmament treaty banning an entire category of weapons of mass destruction (UNOG, n.d.). Article I prohibits the development, production, acquisition, transfer, retention, stockpiling and use of biological and toxin weapons. This applies to all naturally or artificially created or altered microbial and other biological agents and toxins, as well as their components, regardless of origin and method of production and whether they affect humans, animals or plants, *of types and in quantities that have no justification for prophylactic, protective or other peaceful purposes*. Also banned are the weapons, equipment or means of delivery designed to use such agents or toxins for hostile purposes or in armed conflict.

Parties are required to take any necessary measures at the national level to prohibit and prevent the development, production, stockpiling, acquisition or retention of the agents, toxins, weapons, equipment and means of delivery (Article IV). Parties, particularly those with substantial biological defence programmes, have to provide annual reports on specific activities, including: data on research centres and laboratories; information on national biological defence research and development programmes; declaration of past activities in offensive and/or defensive

biological research and development programmes; and information on outbreaks of infectious diseases and similar occurrences caused by toxins (UNODA, n.d.).

BOX 9: **Existing application of the BWC to GMOs**

Advances in the life sciences have been acknowledged to make these technologies inherently 'dual use', meaning that they could be used for both peaceful and malevolent purposes, and there may only be a fine line between the two. Clearly, this applies to genetic engineering and GMOs, making these relevant subject matters for the BWC.

As early as 1986, Parties recognised the "apprehensions arising from relevant scientific and technological developments, *inter alia*, in the fields of microbiology, genetic engineering and biotechnology, and the possibilities of their use for purposes inconsistent with the objectives and provisions of the Convention" (Final Declaration of the Second Review Conference 1986, 3). They reaffirmed that the undertaking in Article I to never in any circumstances develop, produce, stockpile or otherwise acquire or retain microbial and other biological agents and toxins that have no justification for prophylactic, protective or other peaceful purposes, applies to all such developments. Subsequent meetings have reiterated that "Article I applies to all scientific and technological developments in the life sciences and in other fields of science relevant to the Convention" (Final Document of the Sixth Review Conference 2006, 9).

In 2012, advances in genetic technologies such as gene synthesis, synthetic biology and whole genome-directed evolution were discussed. Parties identified the need for enhanced national and international oversight of dual use research of concern (Report of the Meeting of the States Parties 2012, 6-7). In 2013, Parties discussed the need for appropriate oversight measures (Report of the Meeting of the States Parties 2013, 7-8). However, "no concrete steps towards the development of an oversight framework, guiding principles or models to inform risk assessment and oversight of scientific research" have been taken to date (Secretariat of the Convention on Biological Diversity 2015, 93). Moreover, countries such as the United States,

a BWC depository and central BWC actor, have largely relegated oversight of dual use research of concern to voluntary committees composed of professors and researchers.

Parties in 2014 and 2015 discussed various enabling technologies, including genome editing and synthetic biology tools (Report of the Meeting of the States Parties 2014, 7-8; Report of the Meeting of the States Parties 2015, 7-8). They recognised that identifying research of dual use concern necessitates greater national oversight along with a collaborative and informed assessment of the potential benefits and risks. The review of developments in the field of science and technology continues to be on the agenda, where genome editing was identified as a specific topic for discussion in 2018 (Report of the Meeting of the States Parties 2017, 6).

Relevance to gene drive organisms

The potential for malicious use of gene drives has been raised briefly at recent BWC meetings and indeed the BWC is considered the valid international forum for discussion of the security threats raised by gene drives. A presentation on gene drives was made at the Meeting of Experts in 2014, highlighting the potential security challenges (Oye 2014). Among the hostile scenarios envisaged were the use of gene drives to enable a species' ability to host diseases, suppression of crops and livestock in agriculture, or suppression of pollinators and other keystone species, all of which could have devastating impacts.

In the United States, where much of the research into gene drives has been occurring, the national security threat of gene drives has been discussed by the JASONs, a group of elite scientists which advises the US government on national security issues (Callaway 2017). The US Defense Advanced Research Projects Agency (DARPA) has been reported to be the largest funder of gene drive research (Neslen 2017). Another agency, the Intelligence Advanced Research Projects Activity (IARPA), which is part of the Office of the US Director of National Intelligence, is funding work on the national security implications of gene drives, including for detection and monitoring (IARPA 2017).

DARPA states that its 'Safe Genes' project is designed to develop "tools and methodologies to control, counter, and even reverse the effects of genome editing – including gene drives – in biological systems across scales" (DARPA, n.d.). The involvement of the US military in gene drive research has created discomfort, particularly because one strategy used by biodefence programmes is to deliberately create the actual threat itself, with the justification that the activity is necessary in order to learn how to defend against it. The vicious circle of such applied 'threat assessment' results in biodefence activities that are very similar to, and potentially difficult to distinguish from, offensive weapons development (Tucker 2004).

One scientist who has partnered with the DARPA-funded Genetic Biocontrol of Invasive Rodents (GBIRd) consortium has written, "Because the U.S. is funding these initiatives through the Department of Defense, rather than a civilian organization, it's not hard to see how some in the international community may perceive these as potential bioweapons programs, rather than investments in purely defensive technologies" (Kuiken 2017).

GBIRd aims to use gene drives to eradicate invasive rodents on island ecosystems, in order to protect threatened bird species (GBIRd, n.d.). DARPA however has no biodiversity conservation mission, raising questions about the agency's motive in funding research with objectives seemingly outside its mandate. If understood as a threat assessment programme, however, DARPA's motives in promoting GBIRd become clearer – it is a politically more palatable proxy to achieve US national security research.

Freedom of information requests have revealed that GBIRd plans to target the gene drives of specific genetically-defined populations by linking drive activity to the presence of private or locally-fixed alleles – the small genetic differences that define related populations of animals, including humans (Edward Hammond, personal communication, 21 February 2018). The implications of this research (Sudweeks et al. 2019), particularly in a bioweapons context, raise serious concerns. While GBIRd itself may be naively exploring conservation purposes for its gene drives, the dual use implications of population-targeted gene drives

need to be seriously addressed, particularly when DARPA occupies a privileged position as funder, with full access to data and details.

It is clear therefore that gene drives' potential for dual use is established and the BWC is undoubtedly an important international forum to address this.

Limitations

While the BWC, since its entry into force in 1975, sets an important international norm against a particularly egregious form of warfare, it has unfortunately not been able to develop implementation mechanisms or any form of international regulation. It thus provides a forum for discussion, but suffers from a lack of political will by the major powers to actually take action to address the serious issues.

Lengthy efforts to negotiate a binding implementation regime, called the 'Verification Protocol', failed in 2001 (Leitenberg 2002). Most observers regard any return to discussions aimed at the adoption of binding international measures to oversee biological research as politically impossible, for the foreseeable future. There are, simply put, three reasons for this: (i) no appetite among countries with large biodefence programmes to open up their facilities to verification procedures; (ii) strong resistance from industry and other vested interests; and (iii) too many doubts about the reliability of an international inspectorate and the quality of information that would emanate from it (Winzoski 2007).

Thus, while the meetings of the BWC provide a forum for exchange of information on new biotechnologies with security implications, and their confidence-building measures provide limited information exchange, the BWC is institutionally handicapped and impaired from adopting any binding measures pertinent to the biosafety of GDOs.

Nonetheless, serious efforts should be made to ensure that any security threat posed by the misuse of GDOs is able to be more effectively addressed by the BWC, given that it is the treaty with the competence and mandate on these issues.

2.2.5. Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques

Scope, objectives and key provisions

The Convention on the Prohibition of Military or Any Other Hostile Use of Environmental Modification Techniques, also known as the Environmental Modification Convention or ENMOD, prohibits military or any other hostile use of environmental modification techniques having widespread, long-lasting or severe effects as the means of destruction, damage or injury to any other State Party. It is a legally binding treaty that entered into force in 1978 and has 78 State Parties (UNOG, n.d.).

'Environmental modification techniques' are defined as "any technique for changing – through the deliberate manipulation of natural processes – the dynamics, composition or structure of the earth, including its biota, lithosphere, hydrosphere and atmosphere, or of outer space" (Article II).

ENMOD was essentially a response to US tactics used in the Vietnam War, particularly the use of Agent Orange to defoliate forests and thereby deny cover to Vietnamese guerrillas, and attempts at cloud-seeding to cause rain, in order to stymie the movement of people and material during the war. Its design was meant to address modifications to the environment such as defoliants, altering weather, deliberate desertification and deliberate triggering of earthquakes.

To understand ENMOD and how it came about in its final form, including the notorious 'troika' (see below), one must recall the political atmosphere of the mid-1970s. The only countries developing or, in the case of the US in Southeast Asia, using weapons designed to modify the environment were the 'superpowers' (the US and the former Soviet Union) and their close allies. These countries exerted careful control over the ENMOD process, and as a result, the negotiations, while formally based in the UN, did not have the character of a modern multilateral process. Drafts of the Treaty were exchanged between Washington and Moscow, with the two mega-powers agreeing on key details first. Both the US and the Soviet Union wanted to keep a free hand to use certain environmental warfare techniques, particularly in counterinsurgency

(e.g. clearing vegetation in large margins around military bases). Underscoring the faux multilateralism of the process, the last draft was prepared and accepted by Soviet and American negotiators, and then identical texts were submitted by the 'opposing' sides for adoption in Geneva (Pimiento Chamorro and Hammond 2001).

Relevance to gene drive organisms

Gene drives have the potential to artificially modify environments and may be misused for military or hostile purposes (see the discussion on dual use issues in section 2.2.4).

As environmental modification techniques include "any technique for changing – through the deliberate manipulation of natural processes – the dynamics, composition or structure of the earth, including its biota", gene drives that result in population or species changes could arguably qualify as an environmental modification technique under ENMOD. As global gene drives may spread modifications to all populations of a targeted species and potentially result in widespread population changes or population or even species extinction, they may be deemed an environmental modification technique.

Limitations

While ENMOD could possibly be a forum to address military or hostile use of some GDOs, there remain some substantial limitations to the application of this treaty for such purposes. Firstly, it only applies to State Parties and that number is limited. Nonetheless, countries where most gene drive research is occurring, such as the United States and several European countries, are State Parties.

However, ENMOD State Parties have not met recently, and interest in convening mandated conferences of State Parties has waned considerably. The First Review Conference was held in Geneva in September 1984, with the attendance of 35 State Parties. The Second Review Conference took place in September 1992 with very little fanfare and no moves to strengthen the treaty, despite credible and current allegations that Iraq had waged environmental warfare in Kuwait when it set hundreds of oil wells alight (Ross 1992). Attempts by the Secretary-General of the

United Nations in 2013 to convene the Third Review Conference did not receive the required number of affirmative responses in order to proceed (Secretary-General of the United Nations 2014).

Perhaps more significant is the fact that in order to be subject matter under ENMOD, the GDOs in question would have to meet the criteria of being used for military or for hostile purposes, and their effects would have to meet the high threshold of having widespread, long-lasting or severe effects (the so-called 'troika'). While it is certainly possible to imagine a GDO that could have such effects, for example one containing a global gene drive that could cause an economically valuable population or species to become extinct, it is much harder to imagine a nation state using one as a weapon in what would also have to be generally considered a war under international law. Furthermore, efforts to clarify or eliminate the restrictive troika clauses have been made since the original negotiations, as well as at the review conferences; but consensus on removing the qualifiers has not been reached (UNOG, n.d.), leaving the difficult-to-meet troika threshold firmly in place.

Notably, any GDO used as a weapon would be a biological weapon under the BWC, which also prohibits development and stockpiling (except for "peaceful and prophylactic purposes"). Therefore, even before a State Party reached the point of violating ENMOD, which only prohibits hostile use and not development, it would have already violated the BWC. Notwithstanding the limitations under the BWC itself, the BWC would be the more applicable instrument in the case of military or hostile use of GDOs.

2.2.6. United Nations Declaration on the Rights of Indigenous Peoples

Scope, objectives and key provisions

The United Nations Declaration on the Rights of Indigenous Peoples was adopted by the UN General Assembly in September 2007. A majority of 144 states voted in favour, while Australia, Canada, New Zealand and the United States voted against and 11 states abstained. However, the four countries voting against have since reversed their position and now support the Declaration (UN DESA, n.d.). Two abstaining countries

have also since endorsed the Declaration, bringing the current total of supporting countries to 150.

The Declaration, while not legally binding, is the most comprehensive international instrument on indigenous peoples' rights. It establishes a universal framework of minimum standards for the survival, dignity and well-being of indigenous peoples. At the same time, it elaborates on existing human rights standards and fundamental freedoms, as applied to the specific situation of indigenous peoples (UN DESA, n.d.).

Individual and collective rights are addressed, in addition to various provisions dealing with cultural rights and identity, rights to education, health, employment and languages. The Declaration outlaws discrimination against indigenous peoples, promotes their full and effective participation in all matters that concern them, as well as their right to remain distinct and to pursue their own economic, social and cultural development (UNPFII, n.d.).

Relevance to gene drive organisms

Indigenous peoples' rights to the lands, territories and resources that they have traditionally owned, occupied or otherwise used or acquired are strongly protected in the Declaration. Two key principles are reflected in various provisions – that of free, prior and informed consent, and that of redress.

Article 32 of the Declaration focuses on the rights of indigenous peoples in relation to the development or use of their lands and territories and other resources. States are obliged to consult with the indigenous peoples concerned "in order to obtain their free and informed consent prior to the approval of any project affecting their lands or territories and other resources, particularly in connection with the development, utilization or exploitation of mineral, water or other resources" (Article 32.2).

The issue of free, prior and informed consent is particularly relevant to the release of any GDO into the lands and territories of indigenous peoples, or that may affect their resources. For example, gene drive research on the Southern house mosquito is being conducted to address avian malaria in Hawaii, for which the mosquito is a vector, and which

is affecting native birds. It would be feasible to assume that any proposed future release of the gene drive mosquito could occur in the lands and territories of indigenous peoples.

Indeed, this issue was recognised by the AHTEG on Synthetic Biology under the CBD, which pointed out that "a precautionary approach…, taking into account the need for the free, prior and informed consent of indigenous peoples and local communities, might be warranted in the development and release of organisms containing engineered gene drives, including experimental releases, in order to avoid potential significant and irreversible adverse effects to biodiversity" (AHTEG on Synthetic Biology 2017, paragraph 25).

On this basis, SBSTTA, in July 2018, recommended that "…the free, prior and informed consent of indigenous peoples and local communities might be warranted when considering the possible release of organisms containing engineered gene drives that may impact their traditional knowledge, innovation, practices, livelihood and use of land and water" (Recommendation 22/3, paragraph 12).

This recommendation was taken up by COP 14 in November 2018. The decision that was adopted includes the condition that, where appropriate, "prior and informed consent", the "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities should be met when considering the release of GDOs into the environment, including for field trial and research purposes (see section 2.1.1, 'Decision on gene drive organisms at CBD COP 14 (November 2018)').

Should indigenous peoples' lands, territories and resources be confiscated, taken, occupied, used or damaged without their free, prior and informed consent, Article 28 of the Declaration establishes the right of redress for indigenous peoples. States are further required to provide effective mechanisms for just and fair redress for any activities affecting the land, territories and other resources of indigenous peoples, as well as to take appropriate measures to mitigate adverse environmental, economic, social, cultural or spiritual impacts (Article 32.3). In addition, States are obliged to provide effective mechanisms for the prevention of,

and redress for, any action that has the aim or effect of dispossessing indigenous peoples of their lands, territories or resources (Article 8).

This principle of redress is particularly relevant to GDOs and the potential damage they may cause in the lands and territories of indigenous peoples or to their resources, whether the impacts are environmental, economic, social, cultural or spiritual. For example, a gene drive may cause a biological resource that is used by indigenous peoples to become extinct or to not perform as expected, or the modification could lower the value of the resource to indigenous peoples. The general rights of indigenous peoples over their land or territories and resources include that of their productive capacity (Article 29), and to genetic resources and seeds (Article 31). The issue of liability and redress is also a general important issue in the discussion on GDOs (see section 2.1.3).

Limitations

UN Declarations are generally not legally binding in nature, which is a major limitation. However, the Declaration on the Rights of Indigenous Peoples sets forth international legal norms and reflects the commitment of states to move in certain directions, abiding by certain principles (UNFPII, n.d.). These principles are considered universal for indigenous peoples and are important in further clarifying their rights. They can also be the standard by which governments can be called to account on these matters.

The Declaration itself does not create new rights, but provides an interpretation of the human rights enshrined in other international human rights instruments of universal resonance as they apply to indigenous peoples. It is in that sense that the Declaration has a binding effect for the promotion, respect and fulfilment of the rights of indigenous peoples worldwide (UNFPII, n.d.). Therefore, it is important that at national level, governments take action to codify these rights in national law, so as to ensure that these rights are fully respected, protected and fulfilled, including in relation to the impact of GDOs on indigenous peoples and their resources. However, so long as this is not done, then indigenous peoples remain vulnerable to violation of their rights.

2.3. Other guidelines of relevance to gene drive organisms

2.3.1. Guidance Framework for Testing of Genetically Modified Mosquitoes

Scope, objectives and key provisions

In 2009, the World Health Organization Special Programme for Research and Training in Tropical Diseases (WHO-TDR) and the Foundation for the National Institutes of Health (FNIH) co-sponsored a technical consultation meeting to assess GM mosquito technologies. Participants recommended that the World Health Organization (WHO) and FNIH establish a working group to develop a guidance framework for assessing the safety and efficacy of GM mosquitoes, including addressing any legal, ethical, social and cultural issues.

The guidance framework was published in 2014. It proposes efficacy and safety testing standards for GM mosquitoes, in particular a phased testing pathway, with systematic assessment at each step. Four phases are envisaged: Phase 1, laboratory testing including caged trials; Phase 2, field testing under confined conditions which limit release into the environment and which could include geographical, spatial or climatic isolation; Phase 3, staged open release trials; and Phase 4, deployment of GM mosquitoes as a public health intervention (WHO-TDR 2014, 7-10).

According to this guidance framework, any GM mosquito development effort should provide proof of efficacy, acceptability and deliverability. Effective reduction in the transmission of the targeted pathogen(s) should be demonstrated, and the intervention must not be detrimental to the environment and human health. Risk assessment and risk management are core biosafety considerations, with independent ongoing safety review and monitoring during testing recommended.

The guidance framework also examines the fundamental considerations for addressing public engagement and transparency needs in research on GM mosquitoes, as well as questions relating to ethical implications,

including the obligation to respect host communities. The framework reviews existing regulatory requirements and guidance, including that for biosafety, human subjects and GMO regulation. It also discusses additional regulatory considerations such as public consultation, litigation, capacity and institution building, and transboundary movement.

Relevance to gene drive organisms

The guidance framework includes discussion of GM mosquitoes with gene drives, as one of the mechanisms being researched for GM mosquitoes, in order to self-sustain the modification and spread it indefinitely through the target population.

However, the phased testing approach set forth in the guidance framework is, in our view, inappropriate for GM mosquitoes with gene drives, particularly if the gene drive is global in nature and any release into the environment (even in a 'confined' setting, or in geographical isolation as proposed by Phase 2) could mean spread and persistence. Indeed, the AHTEG on Synthetic Biology under the CBD concluded that: "Islands are not ecologically fully contained environments and should not be regarded as fulfilling the conditions in the definition of contained use as per Article 3 of the Cartagena Protocol unless it is so demonstrated" (AHTEG on Synthetic Biology 2017, paragraph 51 (b)). James et al. (2018, 28) further noted that in relation to mosquitoes, "genetic analyses indicate that neither lake nor oceanic islands will provide absolute confinement or inability to spread beyond the island".

Limitations

The guidance framework provides guidelines for testing of GM mosquitoes, including those with gene drives. It is not a legally binding document, nor was it developed intergovernmentally. Many of the contributors could be perceived as having conflicts of interest because they have either self-identified as having professional or even commercial interests in GM mosquitoes (see WHO-TDR 2014, 131).

The guidance framework does not represent the views of the WHO or FNIH, nor does it provide recommendations on what to do. It merely

Table 1: Summary of relevant international legal and regulatory instruments and processes

Instrument	Application	Legally binding?	Number of Parties/ members	Key advantages in relation to gene drive organisms	Key gaps in relation to gene drive organisms
Convention on Biological Diversity	Conservation and sustainable use of biodiversity, fair and equitable benefit sharing	Yes	196	Near-universal membership Already begun to address GDOs Precedence with wider policy issues on GDOs/ new technologies	Lack of implementation and enforcement US not a Party
Cartagena Protocol on Biosafety	LMOs that may have adverse effect on biodiversity, taking into account risks to human health	Yes	171	Subject matter includes GDOs Already begun to address GDOs Specific regulation of GDOs, in so far as they are LMOs	Developed for conventional LMOs Focused on decision-making by a country in the context of intentional transboundary movements Inadequate provision for socio-economic assessment No elaboration of contained use rules Lack of enforcement US not a Party
Supplementary Protocol on Liability and Redress	Liability and redress rules for damage from LMOs	Yes	44	Subject matter includes GDOs Liability and redress rules important for GDOs Damage resulting from unintentional and illegal transboundary movements is included	Damage must result from LMOs/ GDOs from another country Administrative approach places burden on authorities No financial guarantees Limited number of Parties currently US not a Party

WTO Agreement on Sanitary and Phytosanitary Measures	Sanitary and phytosanitary measures that affect international trade	Yes	164	Economic aspects included in risk assessment Ability to take temporary precautionary measures with low likelihood of WTO challenge	Context of trade liberalisation Focused on narrow scientific risk assessment with high tests to meet Limited relevance to GDOs currently
International Plant Protection Convention	Plant pest risks from international trade	Yes* * IPPC itself is legally binding, but its standards are not	183	Applies to plant pest risks from all LMOs, which may be plants, insects, fungi, bacteria, etc. Addresses unintentional pathways of introduction	Limited relevance to GDOs currently
World Organisation for Animal Health standards	Animal health and zoonoses from international trade	No	182	Specific focus on animal health and animal disease agents	Limited relevance to GDOs currently
Biological Weapons Convention	Biological weapons	Yes	182	Mandate clearly addresses hostile use with clear prohibition on development, use and stockpiling for such purposes	No oversight framework on biotechnology research Lack of political will to develop implementation mechanisms
Environmental Modification Convention	Environmental modification techniques	Yes	78	Prohibits hostile and military use	Moribund; limited membership and political will High 'troika' threshold to meet

Table 1: Summary of relevant international legal and regulatory instruments and processes (continued)

Instrument	Application	Legally binding?	Number of Parties/ members	Key advantages in relation to gene drive organisms	Key gaps in relation to gene drive organisms
UN Declaration on the Rights of Indigenous Peoples	Rights of indigenous peoples, including free, prior and informed consent	No	150*	Universal framework of minimum standards, sets international norms Free, prior and informed consent an established right	* Not legally binding, but endorsed by 150 members of the UN General Assembly
Guidance Framework for Testing of GM Mosquitoes	Testing of GM mosquitoes	No	NA	Specific focus on GM mosquitoes	Not developed intergovernmentally Flaws in approach to gene drive mosquitoes

claims to bring together what was known based on research evidence at the time about how best to evaluate GM mosquitoes. However, given that the guidance framework was published in 2014 and the draft was written in 2012, well before any proof of concept for gene drives was demonstrated, it will not be a sufficiently updated reference on gene drive mosquitoes.

Nonetheless, the guidance framework recognises that there is no standardised procedure for addressing potential transboundary movement of gene drive mosquitoes. It acknowledges the need for a "multilateral regulatory process" when it comes to regulation of gene drive mosquitoes, due to the possibility of transboundary spread (WHO-TDR 2014, 99). Specifically, "a regional notification and agreement process may be advisable for planned introductions capable of autonomous international movement beyond the scope of provisions in the Cartagena Protocol" (WHO-TDR 2014, xxv).

2.4. Regulation of contained use

2.4.1. Why contained use regulations are necessary for gene drive organisms

Research and development of GDOs is currently occurring in the laboratory, with no reported releases into the environment yet. According to the US National Academies of Sciences, Engineering, and Medicine (NASEM 2016), gene drive organisms "are not ready for release into the wild" (Abbasi 2016, 482). Yet, there are no stringent international rules on contained use research. As such, this places an increasing onus on ensuring that stringent contained use laboratory research on GDOs is practised and regulated.

The concept of 'contained use' aims to ensure that contact with the environment is prevented by physical means and associated personnel practices. For example, the Cartagena Protocol on Biosafety defines contained use as "any operation undertaken within a facility, installation or other physical structure, which involves living modified organisms that are controlled by specific measures that effectively limit their contact with, and their impact on, the external environment" (Article 3). When these conditions are not met, the situation is therefore one

of 'intentional introduction into the environment', as recently reiterated by the Parties to the Cartagena Protocol (Decision 9/12, paragraph 2). Such conditions are also not likely to be met by 'semi-field testing' in outdoor cages that may be a stage in the development pathway of gene drive mosquitoes (James et al. 2018, 22-25), and hence should not be considered as contained use.

However, the risk of accidental or unintentional release from contained use into the environment always remains, either through laboratory accidents or human mistakes. The novel capabilities of synthetic biology, gene drives in particular (due to their proliferative design), and their potentially increased impacts on biodiversity merit a serious assessment of risks stemming from contained use. A series of recent incidents at high-containment laboratories, including repeated accidental releases by laboratories regarded as being highly professional and secure, draw attention to the inevitability of containment failure. Recent examples include accidental distribution of potentially pandemic influenza viruses by the US Centers for Disease Control and Prevention (CDC 2014a), the discovery of improperly stored and forgotten samples of viable smallpox virus at the US National Institutes of Health (CDC 2014b; Christensen 2014), and numerous incidents of accidental distribution of viable anthrax bacteria by the US Army's Dugway Proving Ground (Chappell 2015).

For GDOs especially, the consequences are great, because even a small unintentional release, particularly of a global gene drive, can result in an extensive spread of the gene drive (Esvelt and Gemmell 2017, 2; Noble et al. 2018; Simon et al. 2018, 3), possibly throughout an entire species. The very properties that make GDOs desirable – spread and persistence – mean that contained use will need to be especially stringent. As such, the safe handling of GDOs in contained use merits special attention. A combination of multiple stringent confinement strategies and safeguards to prevent the unintentional release of gene drive systems from the laboratory has been recommended by leading gene drive researchers (Akbari et al. 2015).

Indeed, that subset of GDOs that are designed to eradicate populations or species (e.g. mosquitoes, rodents) may far more closely resemble dangerous pathogens than other types of GMOs. Such GDOs, currently

under development, are intended to be 'infectious' (through mating), lethal (i.e. severe in consequence), and difficult (probably impossible) to treat or to remove from the environment. They have the capacity, indeed are designed, to spread widely through a population or entire species. These are key characteristics that traditionally define dangerous organisms (usually pathogens) that are assigned to higher-risk groups, and which in turn typically require high-containment facilities and associated stringent personnel practices.

The AHTEG on Synthetic Biology under the CBD has pointed out that the development and implementation of well-designed strategies, which includes physical containment, might be needed for the organisms, components and products of synthetic biology (including GDOs) under contained use, in order to effectively limit their survival or spread and to prevent or minimise their environmental exposure (AHTEG on Synthetic Biology 2017, paragraph 18).

Despite this great need, amply demonstrated by numerous incidences of accidental releases of pathogens in contained use, however, "there are currently no dedicated guidelines on the required risk assessment and minimal control measures applicable to gene drive organisms in contained use" (van der Vlugt et al. 2018, 25).

2.4.2. Contained use regulations at the international level

LMOs destined for contained use are subject to the provisions of the Cartagena Protocol on Biosafety, since its scope applies to the transboundary movement, transit, handling and use of all LMOs (Article 4). However, the Cartagena Protocol does exclude LMOs destined for contained use from its AIA procedure, if the transboundary movement is undertaken in accordance with the standards of the Party of import (Article 6). Nonetheless, the Protocol preserves the rights of Parties to subject LMOs in contained use to risk assessment prior to decisions on import and to set standards for contained use within their jurisdiction.

This all points to the importance of national regulations on contained use for LMOs, which would also be applicable to GDOs, and indeed, many countries already may have such national standards.

However, there are no international contained use regulations or standards, and furthermore, there are none that are specific to GDOs. This is a major gap, especially because of the potential for unintentional releases of GDOs that might result in transboundary movement or the crossing of national borders, requiring an international response.

The need for internationally agreed standards for effective containment of GDOs, in order to avoid accidental releases from laboratory facilities, has been duly acknowledged by the AHTEG on Synthetic Biology (AHTEG on Synthetic Biology 2017, paragraph 51(c)).

2.4.3. Regional standards and other contained use guidelines

Currently there do exist regional standards and other contained use guidelines that provide some useful insights for contained use regulation of GDOs, and their salient features are summarised below. The EU's 'Directive on the contained use of genetically modified micro-organisms' is a regional law for EU member states. There are other non-legally binding guidelines for contained use that have become the *de facto* international standards, although they remain voluntary. These include the WHO's 'Laboratory Biosafety Manual', the US Department of Health and Human Services' manual on 'Biosafety in Microbiological and Biomedical Laboratories', and the US National Institutes of Health's (NIH) 'Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules'.

EU Directive on the contained use of genetically modified micro-organisms

The European Union's 'Directive on the contained use of genetically modified micro-organisms' is a regional standard that is legally binding on EU member states, which have to implement it through their national laws. The Directive is restricted to GM microorganisms, and is therefore largely concerned with the identification of the risks to human, animal, and plant health that could be caused by pathogenic properties. While there are currently no pathogenic GDOs, the parallels with pathogens, as discussed above, necessitate stringent regulations for contained use, in that the aim is to prevent their escape into the environment.

Therefore, the general principles of the Directive are a useful framework for identifying potential adverse effects of GDOs and their likelihood of occurrence, as well as assigning risk classes to a contained use activity with a GDO (van der Vlugt et al. 2018). In addition, the Directive is already applicable to any GDO that is a microorganism in contained use.

The Directive obliges EU member states to conduct a risk assessment of the contained use of GM microorganisms in terms of the risks to human health and the environment. The results are then used to assign four classes of activities, ranging from no or negligible risk and low-risk up to moderate-risk and high-risk, which correspond to four levels of containment. Notification to the competent authority is required prior to any contained use activity, with classes 3 and 4 requiring prior consent or approval from the competent authority. Emergency plans are required to be drawn up before any contained use activity commences.

Member states report regularly on laboratory accidents involving GM microorganisms. In the event of an accident that could affect other member states, there is a regional alert and consultation process. The member state concerned has to alert and consult other member states likely to be affected, on the proposed implementation of emergency plans.

WHO Laboratory Biosafety Manual

The WHO Manual is a reference and guidance document intended to help countries, particularly developing countries, implement basic concepts in biological safety. This is encouraged through the development of national codes of practice for the safe handling of pathogenic microorganisms in laboratories, although there is no obligation for countries to do so. The third edition, published in 2004, adds text on the safe use of recombinant DNA technology.

Inherent in the Manual is the idea of classifying microorganisms according to risk groups[5] and of designating laboratory facilities

[5] Risk Groups 1 to 4, ranging from a microorganism that is unlikely to cause human or animal disease, to a pathogen that usually causes serious human or animal disease and that can be readily transmitted, and for which effective treatment and preventive measures are not usually available.

according to biosafety levels.[6] Biosafety level designations are based on a composite of various factors, such as design features, construction, containment facilities, equipment, practices and operational procedures. Establishing the appropriate biosafety level for laboratory work requires a risk assessment that takes the risk group, facilities available and other factors into account.

The Manual sets out the factors to consider in conducting a microbiological risk assessment and advocates a precautionary approach when there is not enough information available. It details the minimum requirements necessary for all biosafety levels. Comprehensive guidelines are provided for basic laboratories – Biosafety Levels 1 and 2 – as these are fundamental to all laboratories regardless of their biosafety level. The guidelines for Biosafety Level 3 and 4 laboratories modify and add to the basic guidelines, and are designed for work with more hazardous pathogens.

The Manual also sets out guidelines for laboratory animal facilities, including the designated containment levels. These apply the contained use standards to animals that are inoculated with microorganisms from the various risk groups. Additional precautions that are necessary for certain arthropods, particularly flying insects, are also listed. These could possibly be adapted for use in relation to GDOs that are animals or flying insects.

The Manual includes a chapter on laboratory biosecurity, which addresses situations when there is loss, theft, misuse, diversion or intentional release of pathogens and toxins. This is relevant to the dual use issue that is inherent to technologies such as gene drives.

Biosafety in Microbiological and Biomedical Laboratories

The US Department of Health and Human Services publication, 'Biosafety in Microbiological and Biomedical Laboratories', deals with safe microbiological and biomedical laboratory practices. It is an advisory and guidance document recommending voluntary best practices for the safe

[6] Laboratory facilities are designated as: basic – Biosafety Level 1 and Level 2; containment – Biosafety Level 3; and maximum containment – Biosafety Level 4.

handling and containment of infectious microorganisms and hazardous biological materials. Two principles of biosafety – containment and risk assessment – are paramount, aiming to protect laboratory workers, the environment and the public from exposure to infectious microorganisms and to prevent laboratory-associated infections (LAI).

Four ascending levels of containment, offering increasing protection and referred to as biosafety levels 1 through 4, are currently established.[7] The risk assessment process identifies the hazardous characteristics of a known or potentially infectious agent or material, the activities that can result in a person's exposure to an agent, the likelihood that such exposure will cause an LAI, and the probable consequences of infection. The risk assessment guides the selection of appropriate biosafety levels. At each level, the microbiological laboratory practices, suggested safety equipment and facility safeguards are described.

The issue of laboratory biosecurity is also discussed. The objective of biosecurity is to prevent loss, theft or misuse of microorganisms, biological materials and research-related information. A biosecurity risk assessment is recommended to analyse the probability and consequences, while providing the basis for risk management decisions. These elements may be useful to address the dual use potential of gene drives and to safeguard against misuse.

Arthropod Containment Guidelines provide principles of risk assessment, recommend biosafety measures for arthropods of public health importance and address the unique containment challenges. Four Arthropod Containment Levels (ACL 1 – 4) add increasingly stringent measures and are similar to biosafety levels. The Guidelines are relevant to GDOs that are insects, for example, gene drive mosquitoes. As an example, one research project with mosquitoes containing population

[7] Biosafety level 1 (BSL-1) is the basic level of protection and is appropriate for agents that are not known to cause disease in normal, healthy humans. Biosafety level 2 (BSL-2) is appropriate for handling moderate-risk agents that cause human disease of varying severity. Biosafety level 3 (BSL-3) is appropriate for agents with a known potential for aerosol transmission, for agents that may cause serious and potentially lethal infections and that are indigenous or exotic in origin. Exotic agents that pose a high individual risk of life-threatening disease by infectious aerosols and for which no treatment is available are restricted to high-containment laboratories that meet biosafety level 4 (BSL-4) standards (US Department of Health and Human Services 2009, 3).

suppression gene drives reported that the work was conducted in ACL-2 and in a temperate region, which offers some level of protection due to the lesser ability of mosquitoes to survive in such climates (Kyrou et al. 2018, 1067). In our view, however, this may not be stringent enough and clear legally binding standards specific to GDO contained use experiments are still needed.

NIH Guidelines for Research Involving Recombinant or Synthetic Nucleic Acid Molecules

The NIH Guidelines provide guidance for research involving the construction and handling of: (i) recombinant nucleic acid molecules; (ii) synthetic nucleic acid molecules, including those that are chemically or otherwise modified but can base pair with naturally occurring nucleic acid molecules; and (iii) cells, organisms, and viruses containing such molecules. A risk assessment is required, and four risk groups are established according to the pathogenicity of the agents. A final consideration of the risk is then the basis for setting the appropriate containment conditions or biosafety levels for the experiments.

The Guidelines apply to all recombinant or synthetic nucleic acid research within the US, if the research is conducted at or sponsored by an institution that receives support for such research from NIH, including research performed directly by NIH. All recombinant or synthetic nucleic acid research performed abroad that receives NIH funds must also comply. Voluntary compliance is encouraged of those not otherwise covered by the Guidelines and many institutions have reportedly adopted the Guidelines as current best practice.

The Guidelines are meant to be implemented primarily through Institutional Biosafety Committees (IBCs), which comprise researchers at the institution who have differing expertise, along with other stakeholders not affiliated with the institution, who represent community interests in regard to health and the environment. All research involving recombinant or synthetic DNA must be reviewed and approved by an IBC.

Questions have been raised about the effectiveness of the IBC system in the US where it was designed and where it remains the primary institutional-level bulwark against GMO accidents. Numerous instances of IBCs that fail to meet, do not review research proposals, do not identify and review laboratory accidents, and do not report or act to sanction personnel responsible for accidents, have been identified (Race and Hammond 2008).

Whether the IBCs have the necessary expertise or resources to determine adequate containment measures for GDOs remains a concern, more so in the case of their ability to address issues of biosecurity or the intentional misuse of gene drives (Heitman et al. 2016, 175; NASEM 2016, 170). It has however been suggested that NIH could provide additional guidance specific to experiments using gene drive insects (Carter and Friedman 2016, 11).

The biocontainment measures that have been established by these standards and guidelines for pathogens or dangerous biological agents in laboratory facilities, discussed above, provide valuable insight on how nations and other authorities can regulate GDOs in contained use. However, the current situation applied to GDO research in the laboratory, which is dependent on *ad hoc* adaptations of existing contained use standards or guidelines, with no obligation for reporting or inspecting what biosafety levels are actually being used, or for compliance, needs to be urgently remedied. It is imperative that the international community develop and apply effective international, GDO-specific contained use regulations as a priority. The key elements that we view as necessary for contained use regulation of GDOs are discussed further in section 4.1.

Chapter 3

Towards an Effective International Legal and Regulatory Regime

3.1. A proposed home for international governance of gene drive organisms

After consideration of the various relevant treaties, regulatory bodies and other instruments currently in place, it would appear that the CBD and its Protocols are the best overall structure in which to locate development of international law pertaining to GDOs. This would include responsibility for international contained use regulations (addressed in detail in section 4.1), given the potential species and ecosystem implications should escapes from the laboratory occur. The objectives of each of the three CBD instruments are multifaceted, but all of them include in their aims the conservation and sustainable use of biological diversity.

Of course, much more needs to be done to enable these instruments to be effective against the serious threats posed by GDOs, in particular to biological diversity. In fact, the purpose of some gene drive applications is to supress populations, but may result in population and species extinction, which is directly contrary to the objectives of the CBD.

The CBD and the Cartagena Protocol on Biosafety have near-universal application, with the US as the most notable exception. There are currently 196 CBD Parties and 171 Parties to the Cartagena Protocol. The Nagoya – Kuala Lumpur Supplementary Protocol has only recently entered into force, with currently 44 Parties.

It is clear from the overview in Chapter 2 that GDOs are currently covered by the scope of the CBD, the Cartagena Protocol and the Supplementary Protocol, in so far as GDOs are LMOs, and in so far as GDOs are likely to have a significant adverse impact on biological diversity. GDOs have also begun to be specifically addressed by the CBD and the Cartagena Protocol.

As such, the CBD and its Protocols can be said to be already 'seized of the matter'. However, GDOs pose challenges and risks not foreseen when the Convention and its Protocols were negotiated, since 'conventional' LMOs were what the first drafters had in mind. As such, much needs to be done to enable the CBD and its Protocols to adequately address the governance of GDOs beyond governance of LMOs.

The ongoing work on synthetic biology and risk assessment and risk management by the respective AHTEGs is preliminary and this work needs to be taken further. COP and COP-MOP decisions are also necessary to give effect to their recommendations.

In the Cartagena Protocol, work has already been undertaken on other issues particularly relevant to GDO governance: in the AHTEG on Socio-economic Considerations; by the Network of Laboratories for the Detection and Identification of LMOs; and on unintentional transboundary movements of LMOs. Additional work on these issues specific to GDOs should be undertaken further.

COP decisions on synthetic biology, including GDOs, have stressed the importance of the precautionary approach but, it is important to emphasise, have not required mandatory risk assessment, risk management or regulatory procedures specific to GDOs to be in place or undertaken before any release occurs. The time is ripe for the COP to decide on this as well as on any potential suspension of GDO activity, especially considering the absence of binding and effective regulation of GDOs at local, national or international levels to date. The COP 14 decision (14/19) already moves in this direction (see section 2.1.1). As such, implementation of these governance aspects, at international and national levels, should be a priority.

Explicitly locating broader governance of GDOs under the CBD and allocating more specific regulatory governance to the Cartagena Protocol, with the Supplementary Protocol being designed to address liability issues, seems to be the obvious way to begin the serious work of ensuring that there are specific and binding international rules on GDOs.

Critical steps forward which should be initiated urgently include a thorough review of how the provisions of the Cartagena Protocol and the Supplementary Protocol may become actively responsive to the specificities and risks of GDOs.

A number of options with regard to legal form could be identified to address the areas that need to be strengthened to meet the challenges of GDOs. Among those options available under the Convention and its Protocols include amendments to the Convention and its Protocols, new Protocols, new annexes, or COP and COP-MOP decisions. Work can be undertaken in the SBSTTA, new or existing AHTEGs, or any other subsidiary body established by the COP or COP-MOP. These considerations should be part of the review, as the form required should follow on from the function of new or amended rules, as required.

In addition, serious efforts need to be made to ensure that the implementation of and compliance with the CBD and its Protocols are improved. For example, the Cartagena Protocol is extremely weak in monitoring how it is being implemented and whether Parties are in compliance with its obligations. Parties monitor their own implementation of obligations and report on the measures that they have taken to implement the Protocol. Compliance procedures and mechanisms under the Protocol are facilitative and cooperative in nature, which means there is little in the way of enforcement of its provisions and obligations, as well as few sanctions or other consequences if the Protocol's obligations have been violated. For example, there have been failures in the transboundary notification process when GM mosquito eggs were exported/imported between Parties (GeneWatch UK 2014). Despite civil society bringing this to the attention of the Parties concerned and the CBD Secretariat, no action was taken, as compliance measures are only triggered by one Party against another.

Other international agreements, regimes and fora present opportunities for specific aspects of gene drive and GDO regulation. In particular, the issue of potential dual use of gene drive technologies has to be addressed by the BWC, whose mandate clearly prohibits the hostile use of GDOs, and includes development, production, acquisition, transfer, retention, stockpiling and use for such purposes (see section 2.2.4). Furthermore, the UN Declaration on the Rights of Indigenous Peoples rightly sets the international norms and standards on the issue of free, prior and informed consent (see section 2.2.6).

While international laws are legally binding, and this is necessary for establishing legal obligations that are actionable, there are of course limitations in terms of their implementation and enforcement, funding levels (which may be a combination of mandatory and voluntary funds, and may be insufficient), adequate staffing, and so on. Nevertheless, binding international laws that oblige Parties to take action are far preferable to voluntary or self-regulation. At the international level, this usually means that some financial flows and capacity-building efforts begin to occur, and support and infrastructure is provided to assist countries in their implementation. In the case of GDOs, having legal obligations extending beyond moral responsibility would increase the accountability of the research and development that is already taking place, regardless of any current limitations.

3.2. The role of national biosafety laws and national contained use regulations

The Cartagena Protocol on Biosafety is legally binding on the countries that have become a Party to it through their national legal process. Parties to the Cartagena Protocol are legally obliged to take national measures to implement their international obligations (Article 2.1).

In most cases, Parties to the Cartagena Protocol have national biosafety laws, regulations and administrative orders in fulfilment of this obligation. Parties interpret their international obligations and translate these into their national laws, regulations, etc.

The Cartagena Protocol sets minimum standards for biosafety, which means that Parties to the Protocol can regulate LMOs for the protection

of biological diversity more strictly than the Cartagena Protocol. In so doing, however, the stricter biosafety action must be "consistent with" the objective and provisions of the Protocol, and be "in accordance with" the other international law obligations of that Party (Article 2.4).

In practice, many countries have both adapted and added to provisions from the Cartagena Protocol in their national legislation and regulations. Depending on countries' national interests, these laws range from those that are comprehensive, such as the European Union's various Directives and Regulations dealing with all aspects of biosafety, to those that may be narrower in scope and focused only on the minimum standards set by the Protocol.

However, some of the notable non-Parties to the Cartagena Protocol are the US, Canada and Argentina, which are also major producers and exporters of GMOs. This means that these countries are not bound by this Protocol, which creates a significant problem for international-level cooperation and action. This has been a long-standing issue, made worse more recently. At the same time, US participation in international negotiations, for example, has been far from constructive, often undermining the processes and outcomes. In fora where the US is not a Party, procedural rules can limit its influence; however, in fora where the US is a Party, it has the full rights of any Party to engage in the process and negotiate.

GDOs are currently being researched and developed, mainly in the US and Europe. The US has shown no intention to ratify the CBD or its Protocols since they were negotiated, and is very unlikely to do so, either in the current political context or indeed in the foreseeable future. It should be recognised that even if a specific instrument were to be negotiated for governance of gene drives and GDOs, it is highly unlikely that the US would become a Party to it. This is the reality that has to be worked with and around.

In this political context, if the Cartagena Protocol and the Supplementary Protocol are to be made effective to regulate GDOs, corresponding national rules will be the first line of defence for countries against the undesired spread of GDOs from other countries, especially non-Party countries.

If an importing or neighbouring country has national biosafety rules, producers and exporters from all over the world, including from countries which are not Party to the Cartagena Protocol, will have to comply with their national legislation.

That means that while countries that are not Party to the Protocol have no international obligations to ensure that their companies or exporters comply with the national legislation of other countries, the producers and exporters themselves will have to comply with the countries' national rules if they wish to access that market.

Countries that will most require effective national laws, in addition to or in the absence of effective international rules governing GDOs, are those where research and development of GDOs is taking place, along with those countries which are likely to be recipients of GDOs for release. In addition, neighbouring countries in which research and/or release occur will almost certainly be affected. For example, in the case of the Target Malaria gene drive mosquito, contained use research is taking place in Europe, while Burkina Faso is the proposed first location of release, a situation which potentially also affects neighbouring countries in West Africa.

3.2.1. Importance of contained use standards in national legislation and regulation of gene drive organisms

Contained use issues are particularly important in the case of GDOs, as discussed in section 2.4.1.

Contained use is covered by the Cartagena Protocol, but not by the Protocol's advance informed agreement (AIA) procedure – which confers an international right on Parties to make a decision on imports of LMOs for release into the environment prior to shipment – *if* the transboundary movement is undertaken according to the contained use standards of the importing Party.

Some provisions in the Cartagena Protocol explicitly acknowledge the right of Parties to regulate at national level. Contained use is one such provision. The Cartagena Protocol acknowledges the right of Parties to

make domestic decisions based on risk assessment for any contained use imports. It also acknowledges Parties' right to set domestic standards for contained use (Article 6.2). As such, the necessity for domestic standards on contained use is underscored.

No international regulations for contained use have been developed so far, and furthermore, there are none specific to GDOs. This means that domestic rules for contained use are going to be very important, especially with the advent of GDOs. Existing national regulations, if any, would need to be re-examined for their adequacy as they were likely developed with 'conventional' GMOs in mind.

3.3. The Precautionary Principle and Polluter Pays Principle are fundamental

The Cartagena Protocol and the Supplementary Protocol are primarily concerned with the risks posed by 'conventional' LMOs; but the risks posed by GDOs go well beyond them. GDOs carry their own inherent risks beyond those posed by LMOs, which means it is paramount that any regulatory framework for GDOs be underpinned by the Precautionary Principle and the Polluter Pays Principle – as this section details.

The Precautionary Principle is a normative principle that aims to guide environmental decision-making under conditions of scientific uncertainty. It has four central components: initiating preventive action as a response to scientific uncertainty; shifting the burden of proof of a potentially harmful activity to the proponents; exploring alternative means to achieve the same aims; and involving stakeholders in the decision-making process (Kriebel et al. 2001).

Principle 15 of the Rio Declaration on Environment and Development states that:

> In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation.

This is reflected in the preamble of the CBD, which notes that "where there is a threat of significant reduction or loss of biological diversity, lack of full scientific certainty should not be used as a reason for postponing measures to avoid or minimize such a threat".

The Cartagena Protocol on Biosafety additionally reaffirms the precautionary approach in its preamble, and substantively aligns its objective to be "in accordance with the precautionary approach contained in Principle 15 of the Rio Declaration on Environment and Development", in its Article 1.

Precaution is further operationalised in the decision-making procedures of the Cartagena Protocol (Articles 10(6) and 11(8)):

> Lack of scientific certainty due to insufficient relevant scientific information and knowledge regarding the extent of the potential adverse effects of a living modified organism on the conservation and sustainable use of biological diversity in the Party of import, taking also into account risks to human health, shall not prevent that Party from taking a decision, as appropriate, with regard to the import of the living modified organism… in order to avoid or minimize such potential adverse effects.

Precaution is also established as a principle in risk assessment (paragraph 4 of Annex III of the Protocol): "Lack of scientific knowledge or scientific consensus should not necessarily be interpreted as indicating a particular level of risk, an absence of risk, or an acceptable risk."

In the biosafety context, the Precautionary Principle essentially provides the policy space for countries to limit the use and release of GMOs where there is scientific uncertainty with regard to potentially adverse environmental and health effects.The implementation of the Precautionary Principle presupposes the following: that some threat of harm has been identified; that there is scientific uncertainty in relation to the potential harm; and that there are criteria to guide proactive and precautionary measures (Myhr 2007, 459).

The Polluter Pays Principle is affirmed in Principle 16 of the Rio Declaration:

> National authorities should endeavour to promote the internalization of environmental costs and the use of economic instruments, taking into account the approach that the polluter should, in principle, bear the cost of pollution, with due regard to the public interest and without distorting international trade and investment.

The principle places the responsibility on the party producing the pollution to pay for any damage to the environment or human health. It is linked to Principle 13 (Chee 2012, 45), which addresses the issue of liability and redress, calling on States to "develop national law regarding liability and compensation for the victims of pollution and other environmental damage", as well as to cooperate to "develop further international law regarding liability and compensation for adverse effects of environmental damage" that have a transboundary nature.

With respect to GDOs, liability and redress is a clear pillar of biosafety; it ensures that if damage occurs, there will be compensation or redress made to the victims of that damage (see section 2.1.3). The Polluter Pays Principle further delineates who should bear the responsibility for providing that compensation.

Both the Precautionary Principle and the Polluter Pays Principle are principles that underpin environmental law. They are likewise essential to any regulations addressing gene drive technologies and GDOs, in order to ensure that harm is avoided and anticipatory action taken earlier – rather than later in the process – and that there is justice for victims of harm. However, the two principles need to be implemented in national laws, and this has not always been the case. The result is that, in practice, these two important principles may be routinely ignored. The challenge then is to ensure that these principles are effectively put into operation for GDOs. In the next chapter, we turn to the key elements that are fundamental in a binding international legal and regulatory regime that is based on the Precautionary Principle and the Polluter Pays Principle.

Chapter 4

Key Elements for Binding International Governance of Gene Drive Organisms

A legal and regulatory regime that is responsive to the particular challenges posed by GDOs will need to build on existing biosafety law, address the prevailing gaps and put in place specific elements that address these challenges. What follows are some of the key elements that we ascertain are critical and need to be operationalised in any governance and regulatory regime for GDOs.

4.1. Strict international contained use standards specific to gene drive organisms

Any release of a GDO, including a field trial, is a release into the environment. The regulatory distinction is between containment and release. It is essential, as argued in section 2.4.1, that there are strict contained use standards specific to GDOs. This has to be developed at the international level as a priority and complemented by national rules. The standards have to be legally enforceable in order to be effective.

The AHTEG on Synthetic Biology recognised the need for internationally agreed standards for effective containment of GDOs (AHTEG on Synthetic Biology 2017, paragraph 51(c)). COP 14 called for the development or implementation of measures "to prevent or minimize potential adverse effects arising from exposing the environment to organisms, components and products of synthetic biology in contained use…" (Decision 14/19, paragraph 12). Scientists have also recommended that there be "international harmonization of standards for the minimum containment requirements for gene drive mosquitoes" (James et al. 2018, 18).

There are parallels between the responsibility of scientists working in the laboratory on self-propagating pathogens and that of those working with GDOs: both have to ensure that these agents remain in the laboratory and do not escape to the outside world (Akbari et al. 2015, 927). The biocontainment precautions that are set for pathogens or dangerous biological agents in laboratory facilities therefore provide some insight on how to regulate GDOs in contained use (see section 2.4.3).

The basic idea for regulating contained use activities is to set ascending levels of containment, which correspond to increasing levels of protection; these range from the lowest biosafety level 1 (BSL-1) to the highest at level 4 (BSL-4). Applied to GDOs, those GDOs with a high potential for spread or invasiveness, such as those containing global suppression drives, should be subject to higher containment stringency and management procedures (Benedict et al. 2018, 4; van der Vlugt et al. 2018). Current contained use measures, as applied to pathogens, may include some that are not relevant for GDOs, and others that may not provide adequately for the suite of controls necessary to contain GDOs. This means that there is a need to adapt the details accordingly, along with an additional focus on potential environmental hazards due to potential species and ecosystem effects (Simon et al. 2018, 3).

A framework for risk assessment and risk management of GDOs in contained use, involving three risk classes, has been proposed by van der Vlugt et al. (2018). Risk classes are assigned after consideration of the identity and nature of the potential adverse effects on human, animal and plant health and the environment; the severity of the adverse effects (e.g. expected persistence and spread); the likelihood that these adverse effects will occur; and connected to this, the characteristics of the activity with the GDO (e.g. scale of operations). Specific minimum requirements for physical measures and working practices are then proposed for risk management according to the risk classes. Generally, higher-risk activities necessitate additional layers of physical containment, with more stringent access restrictions for the highest risk class, in order to reduce the likelihood of an unintentional release. Risk management measures also include an emergency plan for the highest risk class.

At present, there is no standardised application of contained use standards to current GDO research and development, much less any internationally agreed regulations specific to GDOs. Current projects are adapting existing contained use standards (which range from the lowest biosafety level at BSL-1 to the highest level at BSL-4, or the arthropod containment equivalents) but in our view, too much is left to the individual researchers or their institutions, including the assignment of biosafety levels, monitoring and oversight requirements. This means that existing research may not sufficiently have in place the strict standards that are necessary for GDOs, especially those with global drives capable of potentially eradicating populations. For example, a freedom of information request has revealed testing of population suppression gene drives in New World screwworm in Panama at only a BSL-2 facility (Edward Hammond, personal communication, 12 June 2018).

In our view, some GDOs, depending on their specific modifications, have parallels with pathogens that are classified as subject to BSL-3 and BSL-4 containment and therefore should also be subject to these higher containment standards. Specifically, if these particular GDOs escape, they are difficult or impossible to control and can be expected to have very negative consequences. In particular, research in contained use of gene drive systems that are capable of introducing deleterious or lethal traits requires the same safety level as for pathogens that would have similar effects if released. At least some GDOs would meet these criteria if they could result in widespread population or species extinction.

Multiple strategies are needed, as "any single confinement strategy could fail" (Akbari et al. 2015, 927). These strategies may be molecular, ecological, reproductive or physical. For example, work with gene drives in a location where the species under study is also present (or which it might breed with), even if not necessarily directed toward lethal traits, should be subject to higher biosafety scrutiny, given that even the smallest containment failure could result in introduction of the trait into the wild population(s). To reduce this possibility, it has been recommended that laboratory work with GDOs should not occur in areas where the wild population is present (Akbari et al. 2015, 928). There may be other situations where the wild population may not be present, but the environment is suitable for establishment and persistence of any escapees, which would require more stringent containment measures.

Furthermore, when it comes to insect GDOs, considerations beyond the provision of physical containment need to be taken into account. For example, greater attention is needed to strain management, including its distribution and identity confirmation (Benedict et al. 2018, 4-5; James et al. 2018, 18). This is because contamination within laboratories may happen, for example, of non-transgenic or wild-type strains which are often kept in the same laboratory as references, whereby subsequent transfer to another laboratory of that reference strain may not be appropriately handled at the right biosafety level.

All the above elements should be factored in when devising rules for contained use of GDOs. These regulations must be specific to GDOs, as none currently exist. Furthermore, the necessary oversight of GDO laboratory research is presently too piecemeal and is not sufficiently stringent. A strong case can therefore be made for requiring the licensing of experiments with GDOs in contained use (see Box 10), which would allow for appropriate oversight by the government agencies concerned. This national-level action can be immediately implemented to complement the international rules for contained use of GDOs that are urgently needed.

Working out these specific details for GDOs in contained use requires time and effort and this should be a priority, given that research and development on GDOs is already underway in numerous laboratories around the world. Even if there are no releases of GDOs into the environment, there is a need to urgently address the issue of contained use in research and development, so that the risks of unintentional escape are effectively minimised.

Strict containment measures should also apply to GDOs that are transported, to ensure that there are no escapes at this stage (James et al. 2018, 18-19). In this regard, Article 18 of the Cartagena Protocol on Biosafety relating to handling, transport, packaging and identification of LMOs applies, although to date, no specific international rules and standards exist.

While robust and stringent regulations for contained use are being developed, meaningful public participation is also necessary at all stages

BOX 10: **Licensure**

In addition to generally-applicable biosafety rules, one option to ensure that GDO-specific biosafety requirements are observed, particularly in the context of large research institutions that simultaneously handle many protocols for research involving GMOs, is to require licensure of GDO experiments. Review and approval of GDO contained use applications by a national body enables more thorough, consistent and unified government oversight, and can create an important legal presumption that any unlicensed GDO experiment will be sanctioned, thereby discouraging poorly planned or inadequately equipped experimentation with potential legal penalties.

In addition to creating clarity and even-handed oversight, national licensure enables the creation of review panels that possess specialised expertise in gene drives and GDOs and their implications, a great advantage that is unlikely to be available at individual research institutions. In addition, because in some countries general biosafety rules apply unevenly to research sectors (e.g. exemptions for privately-funded research), by requiring licences for GDO experiments governments can ensure that biosafety loopholes are not exploited and that experiments of which the government is unaware do not proceed.

Finally, given the strong transboundary potential of some GDOs, national-level licensing of GDO experiments places a government in a more informed position, and likely gives it more options and the ability to respond more quickly, if transboundary issues arise, either from domestic research or the spread of an unauthorised GDO from abroad.

and especially at this particular one, so that research and development trajectories incorporate and address citizens' concerns and views from the start. Public engagement was highlighted by the National Academies of Sciences, Engineering, and Medicine as essential and integral to the planning, assessment, and regulation of gene drive research (Heitman et al. 2016, 175).

Due consideration should also be given as to the most appropriate forum for the development of international contained use regulations and/or standards for GDOs (see discussion in section 3.1). Under the Cartagena Protocol, no standards for contained use have been developed thus far. Developing such rules at the international level is therefore a priority.

The most suitable venue for such a process currently would be the CBD and its Protocols, which have clear jurisdiction over GDOs and where discussions in this regard are already advanced. While other fora, such as the WHO, could be involved in the discussions, its remit or sphere of activity is much more limited and would only apply to certain aspects of the technology, such as gene drive mosquitoes deployed for vector control.

At the same time, domestic regulations for contained use remain very important. Existing national rules, if any, would need to be re-examined for their adequacy with regard to GDOs.

4.2. Joint decision-making for intentional release into the environment

4.2.1. State responsibilities

Principle 2 of the Rio Declaration on Environment and Development recognises that state responsibilities in relation to environmental matters extend beyond national jurisdiction: "States have…the responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States or of areas beyond the limits of national jurisdiction" (see Box 11). This principle is reflected wholesale in Article 3 of the CBD.

Furthermore, Principle 14 of the Rio Declaration calls for States to effectively cooperate to discourage or prevent the relocation and transfer to other States of any activities and substances that cause severe environmental degradation or are found to be harmful to human health. Fundamentally, the idea is that there should be cooperation among nation states to ensure there is no relocation or transfer beyond borders of any materials having adverse effects on the environment or health.

BOX 11: **State responsibility under international law**

States have a responsibility under international law to not cause harm in the environment of another State. This obligation is a clear principle of international law. If there are activities that present a risk of environmental harm, States also have an obligation to notify and consult with other potentially affected States. Both actions and omissions may result in States being held liable for violations of their international obligations.

These obligations remain on all States even if they are not a Party to an existing international agreement on liability and redress for a particular environmental harm, such as for damage resulting from LMOs under the Nagoya–Kuala Lumpur Supplementary Protocol on Liability and Redress. A State does not discharge its obligations to not cause harm in the environment of another State by becoming a Party to an environmental liability and redress treaty, even if the responsibility for the activity in question lies with a private entity.

Reference: Nijar 2000.

4.2.2 Joint decision-making

Joint decision-making can range from international rule-making by consensus, where countries make decisions jointly, to decision-making on specific applications by all potentially affected countries, in cases where any unilateral decision involving transboundary implications would be unfair (see Box 12).

Given the transboundary nature of the potential spread and adverse effects of GDOs, a key element in their governance is therefore the need for decision-making by all potentially affected countries (Sustainability Council of New Zealand 2018, 24-27). This means that countries that are affected beyond the country of release must also have a stake in any release decision.

BOX 12: **Joint decision-making in practice**

Making decisions jointly is not an alien concept in international treaties and this is also the case for the CBD and its Protocols. Parties adopt decisions based on consensus, which means that they have to agree jointly when their governing bodies meet. This is also applied to decisions on specific actions in international law, such as those that restrict or ban the use of a substance. For example, the Montreal Protocol on Substances that Deplete the Ozone Layer sets legally binding limits on national production and consumption of ozone-depleting substances, which Parties jointly agreed to. The Stockholm Convention on Persistent Organic Pollutants likewise prohibits, and/or eliminates or otherwise restricts, the production and use, as well as import and export, of certain persistent organic pollutants, the list of which was jointly decided. Both the Montreal Protocol and Stockholm Convention have built-in provisions that set out the procedures by which Parties can add new chemicals to the list of those that are prohibited or restricted, which also requires joint decision-making.

The member states of the European Union practise a version of joint decision-making when it comes to EU-wide GMO approvals.[8] Whether for cultivation or for food and feed purposes, a GMO has to undergo an approval process, entailing risk assessment and decision-making by all member states. A decision to approve or reject a GMO is reached by a qualified majority. If there is no such majority, the European Commission may convene an Appeal Committee. If that Committee fails to reach an opinion by a qualified majority, the Commission then takes the responsibility for the final decision. If there is authorisation, member states can still legally restrict or prohibit GM crop cultivation in their territories or adopt safeguard clauses to address new risks to health or the environment that may be subsequently identified, thus preserving their right to make decisions in their national interest.

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[8] See https://ec.europa.eu/food/plant/gmo/authorisation_en for further information on GMO authorisations in the European Union.

Joint decision-making has also been termed 'collective consent', a concept that recognises that granting approval for certain activities should involve all affected parties (Sustainability Council of New Zealand 2018, 24-27). Applied to gene drives, this means that every country has a right to give or withhold its approval for a GDO release in another jurisdiction that could directly or indirectly impact its territory. Those proposing a release "should be required to seek the prior consent of those nations that are vulnerable to the effects of a gene drive GMO in another jurisdiction or to the flow on effects of a gene drive release elsewhere" (Sustainability Council of New Zealand 2018, 26).

Even gene drive developers recognise that moving forward without the permission of every other country harbouring the target species would be highly irresponsible (Esvelt and Gemmell 2017, 3). They also agree that "regulatory approval must be obtained from every country that would be affected by an eventual deployment" (Min et al. 2018, S52). This is reflected in proposals for a multi-country or regional coordination, authorisation and decision-making process for gene drive mosquitoes (James et al. 2018, 12; James and Tountas 2018, 4793).

Joint decision-making is not about harmonising decisions at a regional level or allowing a regional entity to make a decision on behalf of all the countries; it is about ensuring that every country that is likely to be affected has a right to be consulted and to potentially withhold its approval.

4.2.3. Implementing joint decision-making under the Cartagena Protocol on Biosafety

Under the Cartagena Protocol on Biosafety, the principle of prior informed consent is already implemented through its advance informed agreement (AIA) procedure (Article 7), details of which are elaborated in Articles 8 to 10, and Article 12 (see section 2.1.2).

The governance of movements of LMOs between countries that are Party to the Cartagena Protocol is premised upon obtaining AIA for intentional introduction into the environment of an LMO in another country. The obligation is on the Party of export to either obtain the consent, or require its exporter to obtain the consent, of the receiving Party before

the transboundary movement can take place. If any transboundary movement occurs outside of this agreement, the provisions of Article 17 and Article 25 become relevant. The transboundary movement becomes unintentional and illegal in most cases (see section 4.3).

In the context of GDOs, while AIA remains an important central tenet, joint decision-making would require extended modalities to be able to deal with the specific nature of GDOs and to account for the wider number of Parties that may be involved in a decision. Because gene drives have the propensity to spread genetic modifications in a transboundary manner and at the point of release, their effects cannot necessarily be confined to one country or to a specific import.

Furthermore, because a GDO domestic release will very likely result in spread and transboundary movement, there needs to be consideration of a shift, both in time and space, of when and where AIA is exercised. Essentially, the prior consent should be sought *before* the time and point of domestic release in one country, not at the time when the crossing of the border of another is anticipated or sought, as is currently the case with LMOs.

Detailed arrangements as to how such a system of joint decision-making could be implemented under the CBD and/or the Cartagena Protocol on Biosafety should be considered. Questions of whose consent should be sought for a particular application, what modalities should determine how collective consent is obtained and how far in advance such consent should be obtained, should be carefully considered. Whether or not, and how these details could be codified in the current legal texts or taken up in future decisions of the Parties would be another issue meriting serious discussion.

4.3. Effective measures for dealing with unintentional transboundary movements

Unintentional transboundary movements occur when there is inadvertent crossing of national borders by a GMO. For example, a GM rice variety had only been approved for field trials in China, but entered the food supply (Zi 2005) and was exported, resulting in unintentional transboundary movements to various countries, including the EU.

Since the GM rice variety had not been authorised in the EU, it was also an illegal transboundary movement. This led to the EU imposing emergency controls on all rice products from China (Price and Cotter 2014, 11). These restrictions required consignments to be certified as not containing GM rice and imports subjected to sampling and document checks at the EU port of entry. The measures were first imposed in 2008 and further measures in 2011, resulting in delays and lost export revenue for Chinese rice exporters.

The characteristics of many GDOs make them amenable to unintentional transboundary movements, whether from contained use or from a domestic release. Gene drives are designed to spread genetic modifications in natural ecosystems and will not respect national boundaries. The transboundary nature of gene drives makes it highly possible that there will be unintentional and illegal transboundary movements of GDOs, for which only limited procedures are provided in the Cartagena Protocol. (Article 17 of the Protocol on unintentional transboundary movements and emergency measures and Article 25 on illegal transboundary movements have been discussed in section 2.1.2.)

Near-certain unintentional transboundary movements of high-risk organisms are a key reason why joint decision-making is important to consider for GDOs (see section 4.2). When unintentional and illegal transboundary movements occur, the country into which the GDO has entered will not be able to make its own assessment and decision on organisms that will likely be impossible to recall. Thereby, the central tenets of the Cartagena Protocol – the right of Parties to have their prior informed consent sought as well as to be able to make decisions on LMO approvals based on risk assessment and in accordance with the precautionary approach – would be circumvented.

Even if joint decision-making is successfully operationalised, when potentially affected countries do give their prior informed consent for any GDO release, this would only mean that the transboundary movement is permissible in those countries. There is still a high likelihood that unintentional transboundary movements will occur beyond these countries, to those that were not party to the joint decision. When this happens, procedures are needed to deal with such incidents.

Principle 19 of the Rio Declaration establishes the concepts of notification and provision of information in the case of transboundary environmental effects: "States shall provide prior and timely notification and relevant information to potentially affected States on activities that may have a significant adverse transboundary environmental effect and shall consult with those States at an early stage and in good faith."

Article 17 of the Cartagena Protocol on Biosafety requires Parties to take appropriate measures to notify affected and potentially affected States, the BCH, and other relevant international organisations when it knows of an occurrence (which could also include escape from contained use or during transport) under its jurisdiction that leads or may lead to an unintentional transboundary movement of an LMO. Notifications must be provided as soon as the Party knows of such situations, and relevant information must be communicated to the affected or potentially affected States. Consultations with these States are also necessary in order to enable them to determine appropriate responses and initiate necessary action, including emergency measures.

In the absence of joint decision-making on specific GDO applications, notification, provision of timely information and consultations with potentially affected parties will all be necessary steps for dealing with unintentional transboundary movements. However, these efforts may be too little and too late. Preventative and precautionary measures are first required to address these scenarios, for example by ensuring strict contained use standards (see section 4.1).

Nonetheless, should unintentional transboundary movements occur despite the best efforts to prevent them, Article 17 requires measures to mitigate the effects, if at all possible. These should be further strengthened and could include, for example, a regional or sub-regional rapid alert system that immediately notifies all affected and potentially affected States. Such a rapid alert system is in operation in the European Union, whose Rapid Alert System for Food and Feed shares relevant information between its members and allows collective response (European Commission, n.d.). This system has worked effectively to inform member states about GM contamination incidences in food and animal feed.

Furthermore, effective emergency and response measures are needed, including in a situation where there is damage or sufficient likelihood that damage will occur. This would require consequent links to liability and redress, as well as detection and identification to enable monitoring. There is also a need to adapt existing tools for detection of GDOs as well as to develop new ones. Measures such as these, which would attempt to deal with unintentional transboundary movements of GDOs as effectively as possible, need to be worked out in detail.

4.4. Genuine public participation and free, prior and informed consent

The need for public participation has been recognised in relation to gene drives and GDOs (see, for example, NASEM 2016). Principle 10 of the Rio Declaration on Environment and Development recognises the three interlinked pillars of appropriate access to information: facilitating awareness; participation in decision-making processes; and access to judicial and administrative proceedings. It says:

> Environmental issues are best handled with participation of all concerned citizens, at the relevant level. At the national level, each individual shall have appropriate access to information concerning the environment that is held by public authorities, including information on hazardous materials and activities in their communities, and the opportunity to participate in decision-making processes. States shall facilitate and encourage public awareness and participation by making information widely available. Effective access to judicial and administrative proceedings, including redress and remedy, shall be provided.

Article 23 of the Cartagena Protocol on Biosafety places a clear obligation on Parties to promote and facilitate public awareness, education and participation (including access to information) and also requires mandatory public consultation and disclosure of results of decisions to the public in the decision-making process.

Two other regional agreements – the Aarhus Convention and the Escazú Agreement – on access to information, public participation and access to justice in environmental matters also set out important rights and obligations in relation to this issue (see Boxes 13 and 14).

There are common elements in the aforementioned instruments which establish public participation as a right enshrined in legally binding treaties. Important among these is that they refer to the active provision of information, that is, the right of the public to receive information and the obligation of authorities to proactively collect and disseminate information of public interest, without the need for a specific request. They also refer to the need for public participation across different stages in a process (in policy making, specific decisions, etc.). Obligations are placed on governments to ensure transparency and accountability of responses. As with other international treaties, these provisions need to be implemented and enforced at national levels.

Furthermore, the need to obtain the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities was reiterated at COP 14 as a condition that should be met before any introduction into the environment of GDOs, including for experimental or research and development purposes (Decision 14/19, paragraph 11(c)) (see section 2.1.1).

There are no international guidelines yet for *obtaining* the "prior and informed consent", "free, prior and informed consent" or "approval and involvement" of potentially affected indigenous peoples and local communities, when considering the release of GDOs specifically. However, there are international norms and standards set forth in the UN Declaration on the Rights of Indigenous Peoples (see section 2.2.6) which should be the basis on which any guidelines are developed. The Mo'otz Kuxtal Voluntary Guidelines on which the language of the COP 14 decision is based also provide guidance.

What specific international guidelines in relation to GDOs should look like in practice and how such consent is to be obtained at national and local levels needs to be further discussed and deliberated, drawing also from other experiences of obtaining the free, prior and informed

BOX 13: **The Aarhus Convention**

The UN Economic Commission for Europe Convention on Access to Information, Public Participation in Decision-Making and Access to Justice in Environmental Matters, also known as the Aarhus Convention, is a legally binding treaty that deals specifically with the issue of public participation. It entered into force in October 2001. The Convention covers Parties from the Pan-European region, including Europe, Caucasus and Central Asia, although it is open for ratification by any other country. It has been ratified by 47 countries, including the European Community.

The Aarhus Convention grants the public rights and imposes obligations on Parties and public authorities as regards access to information and public participation. There are three pillars: access to information; public participation; and access to justice. Public participation relies upon the other two pillars: the information pillar, to ensure that the public can participate in an informed fashion; and the access to justice pillar, to ensure that participation happens in reality.

Activities involving GMOs were not initially subjected to the Convention's participation requirements, but were referred to national legislation. However, in 2002, Parties to the Aarhus Convention adopted the Guidelines on Access to Information, Public Participation and Access to Justice with respect to Genetically Modified Organisms. Known also as the Lucca Guidelines, they create a non-legally binding framework that provides guidance on the practical application of the Aarhus Convention's provisions relevant to GMOs.

Efforts for a legally binding approach culminated in May 2005 when agreement was reached on an Amendment that provides a legal obligation for Parties to provide the public with early and effective information, along with a means of public participation, prior to making decisions on whether or not to authorise a GMO release for experimental or commercial purposes. When decisions are made, due account has to be taken of the public participation outcomes. The GMO Amendment is however not yet in force, due to a lack of political will and strong opposition from the Parties which did not want a legally binding obligation.

BOX 14: **The Escazú Agreement**

The Regional Agreement on Access to Information, Public Participation and Justice in Environmental Matters in Latin America and the Caribbean, also known as the Escazú Agreement, was adopted in March 2018. Rooted in the tenets of Principle 10 of the Rio Declaration, it is both a legal instrument for environmental protection as well as a human rights treaty. Not only does the Escazú Agreement address key aspects of environmental management and protection from a regional perspective, focusing on access rights to information, public participation and justice in environmental matters, it also includes the world's first binding provision on human rights defenders in environmental matters. It aims to include those that have traditionally been underrepresented, excluded or marginalised.

consent of indigenous peoples. What the COP 14 decision makes clear is that there should not be an *a priori* assumption of consent, as would be the case with 'opt out' models, for example, which have been suggested for consideration by James et al. (2018, 32) for large-scale field trials of gene drive mosquitoes.

4.5. Adapted risk assessment and risk management approaches with due acknowledgement of their limitations

COP 13 noted that risk assessment methodologies might need to be updated and adapted for living organisms developed through synthetic biology (Decision XIII/17, paragraph 6). The AHTEG on Synthetic Biology reiterated this, further adding that this might be needed to account for a universal lack of experience with the introduction of GDOs (AHTEG on Synthetic Biology 2017, paragraph 41). In addition, "existing risk assessment considerations and methodologies might not be sufficient or adequate to assess and evaluate the risks that might arise from organisms containing engineered gene drives due to limited experience and the complexity of the potential impacts on the environment" (AHTEG on Synthetic Biology 2017, paragraph 44). The

AHTEG further highlighted that risk management strategies might similarly need to be adapted and complemented (AHTEG on Synthetic Biology 2017, paragraph 48).

The novel features of GDOs that make them distinct from 'conventional' GMOs, and hence pose challenges for risk assessment, include: (i) outcrossing and spread of the transgenes as a prerequisite; (ii) transferring the laboratory to the field; (iii) the modification of wild populations as opposed to cultivated plant species; (iv) the transition from indirect (modification against stressors) to direct modification of stressors such as pests; and (v) modification of common goods (Simon et al. 2018). Adaptations to current risk assessment methodologies are therefore needed, in order to conduct rigorous assessments for gene drives that are designed to spread genetic modifications and that may have irreversible impacts. However, such assessments must also be able to indicate when the data are not strong enough to make a decision or when the risks are too high.

In particular, there remains disagreement, including at the AHTEG on Synthetic Biology, as to the utility of conducting the risk assessment in a stepwise manner, that is, from contained use to field trials and finally to open releases, with the results at each step informing the next step of the risk assessment, an approach that is common for GMOs. It is our view that such an approach is not appropriate at this stage of uncertainty about the impacts of GDOs on the environment, as it includes field-testing, which requires the release of GDOs into the environment.

Some scientists have proposed a phased testing pathway moving from contained use to small-scale geographically isolated releases, and then to small-scale and large-scale open releases for gene drive mosquitoes (James et al. 2018; James and Tountas 2018). This is also the approach recommended for GDOs by the National Academies of Sciences, Engineering, and Medicine (NASEM 2016) and others (e.g. Hayes et al. 2018). However, even so-called isolated releases of GDOs (for example, on islands) may lead to further spread (e.g. wind-blown mosquitoes or rats on cars, boats, planes etc.), which is why the AHTEG on Synthetic Biology noted that islands are *not* ecologically fully contained environments (AHTEG on Synthetic Biology 2017, paragraph 51(b)).

For global gene drives, a field trial already represents widespread release because of the propensity to spread, contradicting the intended procedure to keep the field release limited or confined to some extent (Simon et al. 2018, 3). The AHTEG on Synthetic Biology likewise highlighted that "the step of release into the environment might be irreversible", and therefore called for a precautionary approach (AHTEG on Synthetic Biology 2017, paragraph 45). There is consequently a need for substantially more data and modelling, as well as a reconceptualisation of current approaches to risk assessment, including taking into consideration the long-term effects on ecosystems (Courtier-Orgogozo et al. 2017, 879). Other contained use studies such as long-term caged trials in simulated environments or microcosms could also yield useful data, provided that there is strict stringency for effective containment.

Both the COP 14 decision (14/19, paragraph 9) on synthetic biology and the COP-MOP 9 decision (9/13, paragraph 3) on risk assessment and risk management stipulate that before organisms containing engineered gene drives are considered for release into the environment, specific guidance may be useful to support case-by-case risk assessment. The Parties to the Cartagena Protocol will consider, in 2020, whether additional guidance materials on risk assessment are needed for such organisms.

Therefore, it would be prudent and responsible for Parties and other Governments, as well as any would-be developer, to wait until such international guidance specific to the obligations in the Cartagena Protocol is available, before considering any introduction of GDOs into the environment.

4.6. Full assessment of socio-economic impacts including ethical concerns

Gene drives and GDOs are likely to have significant and wide-ranging social, cultural and economic impacts, which should also be the subject of detailed assessment and informed decision-making (Sustainability Council of New Zealand 2018, 31).

The Cartagena Protocol on Biosafety, in its Article 26, establishes the right of countries to take into account socio-economic considerations that arise from the impact of LMOs on biological diversity when making

decisions about LMOs. It is clear that because of the extensive implications of GDOs, both in society and on the environment, a wider consideration of these issues that goes beyond scientific risk assessment is needed. As recognised by the National Academies of Sciences, Engineering, and Medicine, "a comprehensive approach to the development and governance of gene-drive modified organisms will need to go beyond considerations for public health and the environment" (NASEM 2016, 9).

However, the approach offered by the Cartagena Protocol is clearly not enough, as the provision is weak and does not amount to requiring or conducting socio-economic impact assessments. Taking socio-economic considerations into account is not obligatory under the Protocol; it would be up to each Party to do so. There is also a lack of integration with the risk assessment process, with most regulators giving more weight to the assessment of environmental risks. Despite the development of the 'Guidance on the Assessment of Socio-Economic Considerations in the Context of Article 26 of the Cartagena Protocol on Biosafety' by the AHTEG on Socio-economic Considerations, this is still a work in progress.

Examples of national biosafety laws that attempt to incorporate socio-economic and ethical considerations (see Boxes 15, 16 and 17) provide insight as to how countries might ensure that these important issues find a place in biosafety regulation. How to factor in socio-economic and ethical considerations when making decisions on GDOs is therefore a critical aspect of their governance, one that needs further elaboration.

The implementation of socio-economic considerations in these examples varies. For example, Norway has a strict biosafety regime and has not approved any GM crop for cultivation. It routinely takes socio-economic considerations into account in decision-making. On the other hand, in Bolivia, GM soya was approved before the Law of the Rights of Mother Earth came into force. Competing national interests have meant that GM soya is still widely cultivated in Bolivia, due to the strong agribusiness and trade lobby.

BOX 15: **The Norwegian Gene Technology Act and socio-economic considerations**

Section 1 of the Act states that "the purpose of the Act is to ensure that the production and use of GMOs … takes place in an ethically justifiable and socially acceptable manner, in accordance with the principles of sustainable development and without adverse effects on health and the environment."

Section 10 of the Act states that "… in deciding whether or not to grant an application, considerable weight shall (also) be given to whether the deliberate release will be of benefit to society and is likely to promote sustainable development".

The Act also addresses ethical norms and values associated with humans and environmental ethical considerations.

Assessments of sustainability of GMOs apply not just domestically but also globally, and sustainability is recognised as an inter-generational issue. The assessments should include ecological, economic and social sustainability issues, including:

* Is biodiversity affected on a global scale?
* Is the fulfilment of basic human needs like food, shelter and health affected?
* Are emissions of greenhouse gases affected?
* Is the distribution of benefits or burdens between generations affected?
* Is the distribution of benefits or burdens between rich and poor countries affected?

Benefit to society must be assessed prior to an approval, and has a domestic focus. Relevant questions in an assessment of benefit to society include:

* Is there a need for the product in terms of demand or otherwise?

* Will the product solve or possibly contribute to solving a societal problem?
* Is the product significantly better than equivalent products already on the market?
* Does the product create problems for existing production which should be preserved?

Excerpted from "The Norwegian Gene Technology Act and socio-economic considerations", Norwegian Directorate for Nature Management 2011.

BOX 16: **Swiss law and respecting the dignity of living beings**

Switzerland is the only country in Europe that has a constitutional duty to take the dignity of living beings into consideration. Paragraph 2 of Article 120 of the Federal Constitution on 'non-human gene technology' prescribes that in legislating on the use of reproductive and genetic material from animals, plants and other organisms, the dignity of living beings, as well as the safety of human beings, animals and the environment, shall be taken into account. The concept of 'dignity of living beings' has further been related to the value of the individual organism *for its own sake* (Federal Ethics Committee on Non-Human Biotechnology 2008, 3).

The Gene Technology Act limits the scope of the term to animals and plants (Federal Ethics Committee on Non-Human Biotechnology 2008, 3). Article 8 provides for "respect for the dignity of living beings", whereby genetic modification in animals and plants must not violate the dignity of living beings.

Violation is deemed to have particularly occurred if the modification substantially harms species-specific properties, functions or habits, unless this is justified by overriding 'legitimate interests'. Whether the dignity of living beings has been respected is determined by evaluating the severity of the harm suffered by animals or plants against the significance of legitimate interests as identified in the law.

BOX 17: **Bolivian Law of the Rights of Mother Earth**

The Plurinational State of Bolivia adopted the Law of the Rights of Mother Earth in 2010. It is considered to be the first environmental law that gives legal rights to nature.

In 2012 the Government passed a revised version of the original longer piece of legislation: the Framework Law of Mother Earth and Integral Development for Living Well (*La Ley Marco de la Madre Tierra y Desarrollo Integral para Vivir Bien*).

The laws recognise the rights of Mother Earth (*Pachamama*, an indigenous goddess of the Andes) as a whole, along with "all beings of which she is composed". These rights are spelt out in the law: the right to life; to maintain the integrity of living systems and natural processes that sustain them, including capacities and conditions for regeneration; the right to the diversity of life, without being genetically altered or structurally modified in an artificial way; the right to clean water; the right to clean air; the right to equilibrium, such that the interrelationship, interdependence, complementarity and functionality of the components of Mother Earth are balanced, for the continuation of cycles and reproduction of vital processes; the right to restoration; and the right to pollution-free living.

4.7. A technology assessment approach, including consideration of alternatives

Given the discussion in sections 4.5 and 4.6, it would seem that neither a risk assessment alone nor a risk assessment supplemented by consideration of socio-economic impacts is sufficiently adequate for technologies such as gene drives. To this end, Simon et al. (2018, 3) suggest, for GDOs, "a technology assessment approach that goes beyond mere risk assessment and that is generally not foreseen in legislations". Technology assessment is the study and evaluation of new technologies. It "involves the collection, interpretation and evaluation of information and perspectives around contending technological options" (Ely et al. 2011, 7).

Such a technology assessment approach is not new. It was identified as an important issue in Agenda 21, the comprehensive plan for action on sustainable development that was adopted by the world's governments at the UN Conference on Environment and Development (the Rio Earth Summit) in 1992. An essential aspect was the need to build technology assessment capacity "with due regard to appropriate safeguards on the transfer of technologies subject to prohibition on environmental or health grounds" (paragraph 34.26).

This was reaffirmed in the outcome document of the Rio+20 process, 'The Future We Want', in 2012. The section on technology includes a paragraph on technology assessment:

> We recognize the importance of strengthening international, regional and national capacities in research and technology assessment, especially in view of the rapid development and possible deployment of new technologies that may also have unintended negative impacts, in particular on biodiversity and health, or other unforeseen consequences (paragraph 275).

One critical aspect of technology assessment would be consideration of the appropriateness of the technology compared with other means to achieve the same goals or to address a stated problem. A *comparative approach* allows for a comparison of all the approaches that could achieve the same outcomes, and if there is one that is less risky, then this should be the preferred option (Sustainability Council of New Zealand 2018, 29-30). This requires a move away from evaluation of the attributes of a single technology, towards addressing a much broader range of options (Ely et al. 2011, 22). Such a comparison should be done at the start of technology development, when first considering a GDO as a possible response to a stated problem, and throughout any research and development. It would mean that investments and resources are not wasted on gene drives or GDOs if there are less harmful alternatives available or that could be developed and used (Sustainability Council of New Zealand 2018, 30).

Furthermore, as technology assessment has developed tools for feedback loops to society (Simon et al. 2018, 3-4), the issue of public participation

once again would take centre stage. People must have the ability to decide which technologies they want and to provide input to ensure that these technologies meet their needs and priorities. There is also a need to broaden the expertise involved, so that it is not just limited to a small group of experts, but rather ensures that there are multidisciplinary inputs and specifically brings in perspectives of marginalised groups, an approach that tries to ask the right questions from the start (Ely et al. 2011, 21-22).

At the same time, there is a need to open up the outputs of participation exercises to wider governance processes and policy debates, allowing plural policy outputs that recognise multiple perspectives and priorities, while highlighting new options, neglected issues, areas of uncertainty and otherwise marginalised perspectives (Ely et al. 2011, 22-23).

4.8. Rigorous monitoring and detection

In the case of GMOs, monitoring is the systematic approach for observing, collecting and analysing data on potential adverse effects, based on a risk assessment following a GMO's release. Many jurisdictions provide for the monitoring of GMOs. For example, in the European Union, Directive 2001/18 on the deliberate release into the environment of GMOs requires the submission of a monitoring plan in applications for approval. The monitoring plan includes both case-specific monitoring based on the risk assessment, and general surveillance for unanticipated adverse effects.

Monitoring is also an aspect of the Cartagena Protocol on Biosafety. Article 12 allows for reviews of decisions, particularly in the light of new scientific information on potential adverse effects. Article 16 on risk management also indirectly envisages monitoring as well as "an appropriate period of observation prior to intended use".

Annex III of the Protocol further recognises monitoring of the LMO, among other things, as appropriate "where there is uncertainty regarding the level of risk". The source of this uncertainty could be, for example: unanticipated effects on human health or key ecological functions; interactions with future LMOs; changes in management of the LMO; or uncertainty as to whether the conclusions of safety that may have

supported a decision for environmental release are indeed correct (Heinemann and Quist 2012, 2).

The 'Guidance on Risk Assessment of Living Modified Organisms and Monitoring in the Context of Risk Assessment', developed under the Protocol, includes a section on monitoring of LMOs released into the environment. Monitoring was included because it was viewed as important for risk assessment and risk management and because no specific guidance on monitoring is available either internationally or from the Protocol.

The Guidance provides a robust, comprehensive approach for developing a monitoring plan that focuses on what to monitor, how to monitor, where to monitor, how long to monitor, and how to communicate the results of monitoring. It details two types of monitoring: case-specific monitoring to address uncertainties identified in the risk assessment; and general monitoring, to address uncertainties that were not identified in the risk assessment and which could include long-term effects that may be complex, cumulative, synergistic or indirect (Heinemann and Quist 2012, 3).

Article 7 of the CBD also obliges Parties to identify the processes and activities that have had or are likely to have significant adverse impacts on the conservation and sustainable use of biological diversity, and to monitor their effects.

Monitoring could result in withdrawal of a particular GMO from commercialisation because approvals are either time-limited or subject to a review of decisions. However, this is not possible with GDOs, purely for the fact that once released, a GDO cannot be withdrawn in a biological sense (Simon et al. 2018, 2).

Monitoring in the case of GDOs would thus need to take the following approaches: tracking their movements and the potential spread of the trait through populations and across borders and ecosystems; and identifying unintended, harmful impacts during and after a GDO release, impacts that could lead to a change in or revocation of approval (Sustainability Council of New Zealand 2018, 31-32). This type of monitoring would

also be important to fulfil other biosafety functions, such as liability and redress.

Monitoring of GDOs is also dependent on the capacity for detection, particularly of any unintentional transboundary movements, and would be subject to any limits to detection (see section 2.1.2).

4.9. Stringent liability and redress rules

For GDOs, a minimum requirement would be an international civil liability regime with a strict liability standard (see section 2.1.3). Although the Supplementary Protocol's approach is in effect a strict liability approach, it is also, however, an administrative regime requiring response measures to prevent, minimise, contain, mitigate or avoid damage, and/or to restore biological diversity – responses which may not always be feasible because of the persistence and spread of GDOs. It also places a heavy burden on national authorities, without providing the necessary financial guarantees.

The first review of the Supplementary Protocol will include its financial security and civil liability provisions. This will take place in 2023, five years after its entry into force (which was in 2018). It is imperative that the Supplementary Protocol's rules on financial security and on civil liability are addressed at that time, and in a manner that also meets the challenges posed by GDOs.

There is a need for the international community to seriously explore the possible options for providing financial security regarding GDOs, measures which might include compulsory insurance or other financial guarantees, as well as a supplementary compensation fund. Requiring financial security from the developers of GDOs is necessary in order to ensure that adequate redress measures are undertaken in the event of adverse impacts from GDOs. Examples from other treaties on financial security are explored in Box 18. *Such arrangements must be in place before any GDOs are considered for release.* This should be considered in the comprehensive study on financial security that will be carried out and put for the consideration of COP-MOP 10 in 2020.

BOX 18: **Examples from other international liability instruments on financial security**

The Basel Convention's Protocol on Liability and Compensation for Damage Resulting from Transboundary Movements of Hazardous Wastes and their Disposal requires compulsory insurance, bonds or other financial guarantees. Proof of means to address liability must be provided to the State before any transboundary movement can occur. The person who has suffered damage may sue the insurer directly or the person providing the bond or other financial guarantee, although a State can choose not to allow this.

The Convention on Civil Liability for Oil Pollution Damage 1969 (CLC) also requires compulsory insurance or other financial security. The sums are fixed by the CLC and adequate evidence of the insurance or other cover must be provided. The claimant may sue the insurer or the financial security provider directly.

Under the CLC, the owner of a ship is strictly liable with limited exceptions. A ship owner is allowed to limit his liability by constituting a fund. A government which has initially paid for the clean-up costs is entitled to claim from the limitation fund if the State has allowed for this under its national law.

Still, there were concerns that the victims of oil pollution damage might be left uncompensated and that the financial burden on ship owners was too great. A further instrument known as the International Convention on the Establishment of an International Compensation Fund for Oil Pollution 1971 (the Fund Convention) was agreed upon, to provide for an additional source of compensation in the event, for example, that the ship owners cannot pay or the claim exceeds the liability limits under the Convention.

The oil industry contributes to the Fund. The amounts are determined by a formula and are derived from an initial levy and an annual payment. This means that the whole industry shares the costs and ensures that funds are available for clean-up costs in the event a country is unable to bear the costs. It also ensures that no victim goes uncompensated fully.

Reference: Nijar 2000.

Countries do have recourse to their national civil liability laws; however in most cases, no specific civil liability laws with strict liability standards for GMOs or GDOs are in place. Such specific civil liability laws should be a priority for any country in which research and development of GDOs is happening or where potential deployment is planned.

Chapter 5

The Appropriate Response to the Legal and Regulatory Challenges Posed by Gene Drive Organisms

5.1. Taking the time to get it right

The elements discussed in Chapter 4 are not fully in place and urgent efforts need to be undertaken to ensure they are translated into effective rules that are binding on all countries in order to remedy the serious gaps identified, *before* any release of GDOs is even contemplated. Even highly developed countries, let alone developing ones, are simply not equipped as yet to be able to manage gene drive technologies. The current legal and regulatory regime is not able to effectively regulate GDOs in a precautionary manner, and moreover already suffers from the many limitations described in this paper.

For that reason, some parts of civil society have called for a 'moratorium'[9] on any further technical development and experimental application of gene drives, along with any environmental release of genetically-engineered gene drives. Others have proposed a 'constraint period', which would require withholding GDOs from any release into the environment or field trials until global governance arrangements are in place (Sustainability Council of New Zealand 2018, 49-50).

The International Union for Conservation of Nature (IUCN), comprising governments and civil society organisations, adopted a resolution in 2016 that called on its Director General and Commissions to refrain

[9] More than 170 civil society organisations signed a 'Common Call for a Global Moratorium on Genetically-engineered Gene Drives' in 2016. See: http://www.synbiowatch.org/gene-drives/gene-drives-moratorium/?lores

from supporting or endorsing research, including field trials, into the use of gene drives for conservation or other purposes, until an assessment of the implications of the technology and its potential impacts has been conducted (IUCN 2016).

The Norwegian Biotechnology Advisory Board, an independent body appointed by the Norwegian government to advise it on biotechnology issues, recommended a moratorium on the use of gene drives until international regulations for handling and risk assessment are in place (Norwegian Biotechnology Advisory Board 2017, 17).

There is precedence internationally for such pauses in technology development:

- In 2000, Parties to the CBD adopted a decision which recommends that Parties not approve genetic use-restriction technologies (GURTs) for field testing "until appropriate scientific data can justify such testing", nor for commercial use "until appropriate, authorized and strictly controlled scientific assessments with regard to, *inter alia*, their ecological and socio-economic impacts and any adverse effects for biological diversity, food security and human health have been carried out in a transparent manner and the conditions for their safe and beneficial use validated" (Decision V/5, paragraph23). GURTs raised serious concerns because the technology renders seed sterile, thus preventing farmers from re-using their own seed, a practice integral to agriculture, particularly in developing countries.

- In 2008, the CBD requested Parties to ensure that "ocean fertilization activities do not take place until there is an adequate scientific basis on which to justify such activities, including assessing associated risks, and a global, transparent and effective control and regulatory mechanism is in place for these activities; with the exception of small scale scientific research studies within coastal waters" (Decision IX/16, part C, paragraph 4).

- The CBD in 2010 called on Parties to ensure that no climate-related geoengineering activities that may affect biodiversity take place, "until there is an adequate scientific basis on which to justify such

> activities and appropriate consideration of the associated risks for the environment and biodiversity and associated social, economic and cultural impacts, with the exception of small scale scientific research studies…" that are subject to conditions (Decision X/33, paragraph8(w)).

The rationale for having such a similar 'time-out' in relation to GDOs would be to create a pause in terms of releasing GDOs into the environment, including in field trials, therefore allowing the time to work out the details and to operationalise the necessary legal and regulatory requirements, including those applied to contained use. Such regulations should be developed by, for example, relevant UN bodies, ensuring broad international consensus. In our assessment, the CBD and its Protocols are the best place to do this (see Chapter 3).

This period of developing necessary international and national rules for GDOs should also be coupled with robust and meaningful public participation processes, as well as a reconceptualisation of risk assessment and risk management, which should be adapted to purpose them for the challenges and data limitations posed by GDOs. The right of communities or countries to *withhold their consent* also needs to be respected at all times.

Taking the time to get things right should not be construed as stopping the technology. Indeed, getting it wrong – releasing GDOs before appropriate regulation is in place or settling for insufficient governance – may be more costly, time-consuming and politically challenging than the front-end effort to get the settings right. Gene drive developers estimate that "any unauthorized release of a gene drive system would quite likely delay applications by a decade or more" (Esvelt and Gemmell 2017, 4), and "…inappropriately conducted field trials have the potential to negatively impact the future success of other gene drive products; to undermine community, stakeholder, and/or public confidence in the technology; and to contaminate the regulatory and funding environment" (James et al. 2018, 9).

5.2. What the CBD decision entails

The Parties to the CBD at COP 14, in November 2018, considered

language calling on Parties and other Governments, in accordance with the precautionary approach, to "refrain from the release, including experimental release, of organisms containing engineered gene drives". While no explicit moratorium was decided upon at COP 14, strict precautionary conditions have been spelt out. They should be met before any introduction into the environment of GDOs, including for experimental or research and development purposes. The precautionary conditions stipulated directly in the COP 14 decision (14/19) relate to (i) carrying out risk assessments; (ii) having in place risk management measures; and (iii) obtaining the free, prior and informed consent (or equivalent at national level) of potentially affected indigenous peoples and local communities (see section 2.1.1).

That decision also recalls previous COP decisions that laid out additional elements. These collectively include:

- effective regulatory systems consistent with the principle in international law of States' responsibility to ensure that activities within their jurisdiction or control do not cause damage to the environment of other States (which is very relevant to GDOs given the high potential for transboundary spread);
- addressing issues such as food security and socio-economic considerations with the full participation of indigenous peoples and local communities;
- establishing the right to take precautionary measures (which could include bans and moratoria), even in a situation where scientific knowledge is lacking;
- environmental impact assessment and allowing for public participation in such procedures;
- dealing with the consequences of extra-territorial impacts by promoting reciprocity, notification, exchange of information and consultation;
- immediate notification as well as action to prevent imminent or grave danger or damage beyond national jurisdiction;
- emergency responses and international cooperation for joint

contingency plans when there is a grave and imminent danger to biological diversity; and

- examining liability and redress, including restoration and compensation for damage to biodiversity.

Taken together, the Parties to the CBD have effectively raised the bar for any releases into the environment of GDOs. Most importantly, the international community has pointed to the serious issues that must be addressed before any releases are even considered. This would mean that there has to be requisite time set aside to deliberate, and adequate processes put into place, to properly address these precautionary conditions.

The CBD decisions place implementation obligations on Parties, to which the United States – a non-Party – and any would-be developer who wishes to be seen as operating in good faith should adhere. Gene drive research and development is not an unregulated space that can be experimented in at will. In practice, it is simply not acceptable to the international community for anyone to release a GDO without properly addressing the issues that Parties to the CBD have laid down. Neither would it be right for one country to approve a release without the consent of other potentially affected countries and the local communities concerned.

5.3. Critical steps forward

In order to allow for the space and time to put in place legally binding governance arrangements at the international level, which should include the establishment and operationalisation of the elements identified in Chapter 4 and build on the CBD decisions, the following are critical steps forward in the interim:

Firstly, there should be **no intentional releases into the environment, including field trials, of any GDO**. While there have been calls for a 'phased testing approach' for GDOs, for example by the US National Academies of Sciences, Engineering, and Medicine, which recommended proceeding with laboratory research and highly controlled field experiments (NASEM 2016), there still remain serious concerns at

the intergovernmental level about any release into the environment of GDOs, however small or isolated, as evidenced by the recent COP 14 decision (14/19) putting in place strict precautionary conditions.

For there to be well-considered, internationally-agreed rules and procedures for the governance of gene drives and GDOs, there has to be a thorough pause during which no field trials are conducted, because even small or isolated releases of GDOs can spread, thus defeating the purpose of this important waiting period.

Secondly, there should be **strict contained use standards applied to existing research and development in the laboratory, as well as strict measures for any transport of GDOs, to prevent escape**. The best available standards should be applied immediately while an intergovernmental process should be established to develop mandatory international laboratory safety standards for contained use research involving GDOs.

At the same time, there should be full transparency regarding ongoing research projects; a register should be established and maintained to keep track of developments. This could be done under the CBD's auspices, particularly through the horizon-scanning process that is envisaged for synthetic biology developments. At the national level, governments can improve oversight by requiring the licensure of experiments with GDOs in contained use.

Thirdly, **monitoring and detection for unintentional releases and unintentional transboundary movements of GDOs have to be conducted during this period, with emergency response plans in place.** This has to be done by both the authorities that have oversight and by entities conducting the research and development. Such monitoring is necessary, as unintentional releases may occur at any time and governments should remain vigilant even during a period where no environmental releases are officially permitted. The tools and materials for detection of unintentional releases of GDOs must be quickly developed and/or adapted, in order to enable effective and timely detection and identification.

Finally, the **international rules for this period of constraint, including for their enforcement and for liability and redress should there nevertheless be damage, must be effectively operational, including at national level.** This is necessary because even during such a pause period there is a need for enforcement and to ensure that any unintentional and also rogue releases are adequately dealt with, particularly if any damage results.

Giving pause will allow governance arrangements at the international level to be established and made operational, including mechanisms for joint decision-making by all potentially affected countries. All governments need to engage in fully informed discussions about the seriousness of this issue, aided by the relevant expertise and genuine public participation. In addition, the issue of dual use of gene drives must be effectively addressed at the appropriate fora. Ultimately, political will is required to ensure that the world puts in place effective, legally binding and enforceable rules that are necessary for gene drive technologies.

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There is an urgent need for effective international and legally binding regulation of gene drive organisms (GDOs). Existing biosafety rules, established for 'conventional' genetically modified organisms (GMOs), are deficient and not fully equipped to manage the unique risks of GDOs. With GDOs, spread and persistence are their *raison d'être*, posing different legal and regulatory challenges, because of their high potential to spread beyond national borders, particularly in the case of GDOs containing 'global' gene drives.

This paper reviews existing instruments and processes relevant to gene drives and GDOs, and finds serious gaps. In the authors' assessment, the Convention on Biological Diversity (CBD) and its Protocols, whose aims include the protection of biological diversity, whose scopes include GDOs and which have begun substantive work specific to GDOs, are currently the best home for their international governance.

The paper also sets out elements considered fundamental in a legal and regulatory regime for GDOs. It calls for these elements to be translated into effective rules that are binding on all countries in order to remedy the serious gaps identified, before any release of GDOs is even contemplated. To allow for the space and time to put in place legally binding governance arrangements at the international level, there should be no intentional releases into the environment, including field trials, of any GDO in the interim. At the same time, strict contained use standards should be applied to existing research and development in the laboratory, monitoring and detection for unintentional releases and unintentional transboundary movements have to be conducted, and international rules for this period of constraint must be effectively operational.

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