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Gene Drive: Regulatory, Legal and Ethical Issues

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Background: Technology, Applications & Technical Safeguards

Gene drives force a gene to spread through a sexually reproducing population much more rapidly and to a greater extent than is predicted by standard evolutionary processes.[1] The existence of gene drives in nature has long been known and studied, but recent developments in molecular tools have enabled construction of versatile, 'synthetic' gene drives. One such system was described by Austin Burt in 2003,[2] but very recent advances in site-specific genetic engineering using a tool called CRISPR/Cas9 (and related techniques) have rendered gene drive engineering significantly quicker and easier.[3] This has resulted in renewed interest in harnessing gene drives for population control. Although many of the molecular tools are from bacteria, gene drives cannot be used in bacteria and viruses as these organisms reproduce asexually.

An organism inherits one copy of a gene from each parent. CRISPR/Cas9 and related systems can be used to design a genetic system that 'drives' by cutting its own position on the non-transgenic second copy, resulting in DNA repair using the gene drive-encoding insertion as a template. In these cases, cells with only one copy of the gene drive, known as heterozygotes, will now have two copies and become homozygotes. If this occurs in germ line cells then 100% of offspring will inherit the drive and any associated genes, as opposed to the expected 50% if the organism remained heterozygous. This process repeats within the population until the gene spreads at a rate far above that predicted by classical Mendelian inheritance. This inheritance pattern can result in rapid proliferation of the gene through a population, even overcoming some negative selection and in some cases very strong selection, for example where the trait being driven is female infertility.[4]

Gene drive is most efficient in populations with a short generation time as effects on the population will be seen most rapidly, therefore insects and lab model organisms are effective targets whereas traits would take much longer to spread in longer-lived species.

Technologies related to synthetic gene drive

CRISPR and Cas9 are used in many genome editing techniques where they are expressed transiently in a cell or one is stably inherited and the other provided as required. Gene drive systems involve stable inheritance of both elements and there is a small risk that if both components are inserted into a cell on the same piece of DNA with the intention of editing the genome, homologous recombination could cause them to integrate with the host DNA and potentially lead to a gene drive.[5] Managing the risk of unintended gene drives thus extends to a much broader population of researchers than those actively developing gene drive technology.

There are also examples of non-GM gene drives which are under development and in active field release but come under less regulatory scrutiny.[6] The major example involves the bacteria, *Wolbachia,* which is inherited through the maternal line in many insect species. In mosquitoes, certain strains of *Wolbachia* confer a reproductive advantage to infected females, which causes rapid spread of the strain through populations.[7] Some of these *Wolbachia* strains also have useful properties for population and disease control, including stopping mosquitoes transmitting dengue.[8] As a non-GM technology, the regulation of *Wolbachia*-

based gene drives is very different to those created by CRISPR/Cas9 although the functionality and effects of the technology are very similar.[9] This raises the first of many questions for the regulation of gene drive: should the regulation of gene drive apply to GM and non-GM technology? Somewhat ironically, most of the technical safeguards for CRISPR/Cas9 gene drives (discussed below) are not applicable to *Wolbachia*-based systems.

Examples of existing and proposed applications

Examples of existing CRISPR/Cas9 gene drive include: spreading malaria-parasite resistance in lab populations of the vector *Anopheles stephensi*;[10] and causing female progeny of the related *Anopheles gambiae* to be infertile.[11] Gene drives may be useful techniques for controlling the spread of numerous other vector-borne diseases. Some suggestions to date include altering *Aedes* mosquitoes to reduce transmission of Zika virus;[12] fresh water snails to reduce transmission of schistosome;[13] and white-footed mice to reduce transmission of Lyme disease.[14]

CRISPR/Cas9 gene drives also hold promise for other purposes. The recent National Academies of Sciences, Engineering and Medicine Report ('NAP report')[15] proposed a number of possible future gene drives aiding conservation, agriculture and basic research.[16] At this stage all these proposals are theoretical proposals rather than technology in development.

Important technical features of gene drives from a regulatory perspective

The key features of gene drives which differentiate them from other GM technologies and could potentially require a different regulatory approach are:

Rapidity – spread can be very quick in species with small generation times even with a small number of released GM individuals. This means that effects, including unintended or harmful ones, could reach a wide geographic area before it is possible to respond to them.

Potential for irreversibility – although there are technical safeguards as discussed above, the effectiveness of gene drives is challenging to assess and some may be difficult to reverse leading to a permanent population change. Impacts on the environment or health that take place before any reversal can be effected may also be permanent.

Population-wide effects – whole populations are affected which exacerbates issues around geographic borders, biodiversity and control beyond those that already exist for other GMOs.

Unintended creation – the potential for unintended creation and release of a gene drive system was very small before CRISPR/Cas9 and related technologies but is now a risk that needs consideration.

Technical safeguards

Given the potential of the technology to alter populations rapidly and permanently, various technical safe-guards have been proposed in the event of inadvertent release or unintended consequences.[17] One of these is a "reversal drive"[18] which drives the original sequence back into the population through the same gene drive mechanism. Reversal drives present a promising safeguard. However, there are at least three points of caution that should be noted: public confidence in and attitude towards any reversal drive (after an unsuccessful primary drive) may provide a substantial barrier to release; even if a reversal drive were to reach all members of the population, any ecological changes caused by the primary drive would not necessarily be reversed; and reversal drives will not reverse damage to human, animal or environmental health that has already occurred.

An immunization drive is a gene drive capable of *blocking* the spread of another gene drive by modifying its target site. This is helpful to prevent a specific, unwanted drive from operating on some organisms and can be paired with a reversal drive so that the original sequence is almost entirely restored (some slight modifications will remain). Immunizing reversal drives could be developed and released either pre-emptively or reactively and would spread on a timescale comparable to that of the unwanted drive. However, as with the standard reversal drives above, any ecological changes caused by a primary drive would not necessarily be reversed.[19]

Daisy chain gene drives are a way of designing CRISPR-Cas9 gene drives that "offer a way to alter the traits of only local populations in a temporary manner".[20] Daisy chain gene drives consist of multiple components which are inserted throughout the genome of target organisms but, the initial component of this system is not driven along with the gene drive and therefore the rate of spread is constrained (for further detail, see here). Daisy chain drives are not without risk — a small possibility exists for the components of the drive to be recombined next to each other, thereby creating a 'daisy necklace' capable of operation like normal gene drives.[21] However, researchers suggest that this risk may be overcome by increasing the number of components in the gene drive. For this reason, 5-component drive systems are currently being developed.

Regulatory Systems

As synthetic gene drive organisms have been genetically modified,[22] the main regulations that apply to them are those covering genetically modified organisms (GMOs). Other areas of regulation may apply to some uses of / work with gene drive organisms, these include broader environmental protection and health and safety rules. For brevity, these other areas of regulation will only be addressed when necessary.

EU GMO Regulatory System

Overview

The main components of EU GMO legislation are Directive 2009/41/EC on the contained use of genetically modified micro-organisms and Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms.

The Directives are designed to minimise risks to human health and the environment, making use of risk assessments to identify any necessary measures to reduce risks to a negligible level. Some contained uses require prior notification to a competent authority.[23] All deliberate releases require prior authorisation – with different processes applying to commercial releases and non-commercial releases (e.g. field releases for research and development purposes).[24]

Authorisations for non-commercial release apply only to the territory of a particular member state, and are issued by that state's competent authority. Authorisations for commercial release apply throughout the EU, and are subject to a centralised authorisation procedure.

Contained Use

Directive 2009/41/EC on contained use applies only to genetically modified micro-organisms (GMMs), however some member states have extended the scope of their contained use regulation to cover other GMOs. The Directive utilises a classification system largely based on potential pathogenicity. This means that there is a significant gap in relation to gene drive organisms, which will generally neither fit the definition of GMMs nor present risks based on pathogenicity.

For contained use the main purpose of risk assessment is to identify the containment and control measures necessary to minimise contact between GMMs, humans and the environment, including through accidental releases. The risk assessment should: identify any harmful effects; describe characteristics of the activity; and evaluate the severity and likelihood of the potentially harmful effects.[25] Selection of containment and control measures should be based on the level of risk associated with the GMM, the characteristics of the activity, and the characteristics of the environment likely to be exposed.[26]

Deliberate release

For deliberate release, the main purpose of the risk assessment in Directive 2001/18/EC is to identify any measures necessary to ensure that the release is safe for humans and the environment. The environmental risk assessment should: identify characteristics that may cause adverse effects; evaluate the likelihood and potential consequences of each adverse effect; estimate the risk posed by each characteristic of the GMO associated with a potential adverse effect; outline a risk management strategy; and determine the overall risk.[27] Annexes II-IV of the Directive outline information required in the application for authorisation ('notification'). This includes information on the potential of the GMO: becoming persistent and invasive; having selective advantage; resulting in gene transfer; impacting target and non-target organisms; and affecting human or animal health.

It is generally expected that a commercial release would follow earlier stages of deliberate release (following the 'step-by-step' principle), which would contribute evidence for the risk assessment.

UK GMO Regulatory System

Some aspects of GMO regulation in the UK are administered separately in different countries (e.g. Scotland), while they adopt similar approaches, the specific details here are drawn from their application in England. Following the EU legislation, regulation of GMOs in England is separated between contained use and deliberate release.

Contained use

The Genetically Modified Organisms (Contained Use) Regulations 2014, alongside parts of the Environmental Protection Act (EPA) 1990 require risk assessment and the application of containment and control measures for both GMMs and 'larger GMOs' (any genetically modified organism that is not a micro-organism).

The GMO (Contained Use) Regulations require assessment of risks to human health and the environment for work on GMMs, and like Directive 2009/41/EC use risk classification largely based on potential pathogenicity. The Regulations also require assessment of the human health risks for work with larger GMOs, including a requirement for notification to the competent authority[28] where such GMOs pose greater risk to human health than their non-modified parental organism. The EPA requires environmental risk assessment for work with larger GMOs, but does not specify particular requirements for the assessments. The Scientific Advisory Committee on Genetic Modification[29] advises use of the requirements outlined in Schedule 4 of the Contained Use Regulations in such cases.[30]

The inclusion of risk assessment requirements for contained use of larger GMOs avoids the gap in Directive 2009/41/EC. However, the requirements may not be well adapted for gene drive organisms, and there appears to be a gap in regard to notification to the competent authority where larger GMOs pose environmental risks, but not increased risks to human health.[31]

Guidance provided by the Scientific Advisory Committee on Genetic Modification (SACGM) on contained use of GM animals outlines examples of 'activities likely to raise safety issues' relating to "work with GM animals that are able to persist or become established in the environment" some of which seem particularly relevant to gene drive organisms. These include: "GM animal species likely to disturb natural ecosystems, especially derivatives of naturally occurring species that may have a selective advantage" and "GM derivatives of non-indigenous species that are able to become established".[32]

If the risk matrix outlined in the SACGM Compendium (reproduced below) is utilised this may place work with gene drive organisms within the modest or high risk category, because of the identified hazards relating e.g. to persistence. This would require control measures to be implemented in order to reduce environmental risk to a low or 'effectively zero' level.[33]

		Likelihood of hazard			
		High	**Medium**	**Low**	**Negligible**
Consequence of hazard	**Severe**	High	High	Medium	Effectively zero
	Modest	High	Medium	Medium/low	Effectively zero
	Minor	Medium/low	Low	Low	Effectively zero
	Negligible	Effectively zero	Effectively zero	Effectively zero	Effectively zero

Table 5.2.1 Risk determination matrix

Health and Safety Executive (HSE) guidance on the Contained Use Regulations outlines the following key steps for risk assessment: hazard identification; assignment of provisional risk level; characterisation of the contained use; adjustment of the risk level; selection and subsequent review of containment and control measures.[34] It is also recommended principles of occupational and environmental safety, outlined in Schedule 7 of the Regulation be used for work with GMOs.

Deliberate release

The Genetically Modified Organisms (Deliberate Release) Regulations 2002 and provisions of the Environmental Protection Act cover the procedures for commercial and non-commercial releases. All such releases require authorisation. For non-commercial releases within national territory, applications for authorisation are evaluated by the Secretary of State for Environment, Food and Rural Affairs, with advice from the Advisory Committee on Releases into the Environment.

For commercial releases, where the first release is intended to be in England, the application for authorisation is submitted to the Secretary of State, who will evaluate the application and provide a report to the European Commission, including an opinion on whether the release should be authorised. Risk assessments for risks to human health and the environment must accompany the application for authorisation (along with other information detailed in Schedules 1-4 of the Regulations). The risk assessment requirements are those found in Annex II of Directive 2001/18/EC (described above).

Functionality of GMO regulatory systems

There has been broad criticism of the functioning of EU GMO regulatory systems in practice[35]. Some of the criticism focuses on problems in the implementation of the central authorisation procedures for commercial release, including extensive delays and uncertainties about processing of applications, and political interference in the process.[36] Other criticisms relate to the risk assessment requirements – particularly that the assessment is done against an unrealistic risk free alternative, and does not incorporate consideration of benefits. The latter points are likely to apply to some national systems as well.

International aspects

Particularly at the stage of deliberate release, current proposed uses of gene drive organisms have the potential for transboundary movement and are likely to take place in countries that fall outside of the regulatory systems outlined above. Key considerations for such cases of deliberate release include:

- Understanding of other countries' regulatory systems, and identification of relevant regulatory authorities;
- Adaptations of risk assessment for different environmental conditions; and
- Additional needs e.g. in terms of risk assessment, authorisation, monitoring, etc. where there is potential for transboundary movement of organisms.

Some guidance, e.g. on risk assessment for transboundary movements of GMOs, may be drawn from the Cartagena Protocol on Biosafety to the Convention on Biodiversity (CBD). The CBD also has processes for assessing relevant scientific and technological developments.[37]

Other international organisations that might address certain aspects of work with gene drive organisms include:

- The World Health Organisation – e.g. through development of its Guidance Framework on Testing Genetically Modified Mosquitoes;[38]
- The Food and Agriculture Organisation – where there may be lessons from release of insects modified through nuclear techniques, and also from work on pest risk analysis under the International Plant Protection Convention; and
- The World Animal Health Organisation, which provides guidance on surveillance of arthropod vectors of animal diseases,[39] invasive animals,[40] and biosafety and biosecurity in veterinary laboratories.[41]

DISCUSSION POINTS

Identifying regulatory problems

To what extent can components of existing GMO regulation adequately cover gene drive organisms?

Risk assessment:

Are the definitions of GMOs sufficiently broad in scope?

Are risk classification systems appropriate?

Are risk assessment methodologies and approaches adequate at the different stages of laboratory research, field trials, and commercial releases? Why / why not?

Risk responses:

Are information and notification requirements adequate?

Are there ways in which monitoring systems might need to be adapted?

Are there any gaps in enforcement of current regulatory requirements?

Responding to regulatory problems

For the problems identified in discussion of the points above:

How should GMO regulation (and other areas of regulation) be adapted? What additional information / data is needed in order to propose appropriate reform?

Are there areas of regulation that should be amended as a matter of priority? (For example, contained use).

For problems identified in the functionality of existing GMO regulation:

Is it possible to incorporate consideration of benefits within existing risk assessment processes?

Is there value in moving to a trait-based system of regulation?

Is there any value in testing the current EU regulatory system through a UK government supported field trial of GM insects?

Is it preferable to address these problems by adapting the current regulatory framework?

Is there a need for additional guidance or new regulations?

What do the issues surrounding gene drive regulation tell us about regulation of emerging technologies more generally?

Glossary[42]

Biosafety: Policies and practices intended to prevent harm to the health or safety of human be- ings, other living organisms, or the environment, especially those pertaining to safe handling and containment of infectious agents.

Biosecurity: An integrated system of best scientific practices, environmental controls, and policy and regulation that identifies and manages risks of intentional misuse of technologies, particularly biological agents and processes, in ways that threaten public health or national security.

Conservation: The protection and preservation of the natural environment or particular species, including the maintenance of habitats and genetic diversity.

Containment: The use of human-made or natural physical restrictions to prevent unintended or uncontrolled release of an organism into the environment.

CRISPR (Clustered regularly-interspaced short palindromic repeats): A naturally occurring mechanisms of immunity to viruses found in bacteria that involves identification and degradation of foreign DNA.

CRISPR/Cas9: A gene editing platform in which an endonuclease and a guide RNA are used to introduce double strand breaks at a specified location within the genome.

Ecosystem: A dynamic biological system consisting of all of the organisms in a specific environment and the non-living features of the environment with which they interact.

Field trial: An experiment designed to test a promising new product or process in a context similar to that in which the product or process is intended to be used.

Gene: a segment of DNA that serves as a basic unit of heredity.

Gene drive: A system of biased inheritance in which the ability of a genetic element to pass from a parent to its offspring through sexual reproduction is enhanced. Thus, the result of a gene drive is the preferential increase of a specific genotype that determines a specific phenotype from one generation to the next, and potentially throughout a population.

Gene editing: A technique that allows researchers to alter the DNA of organisms to insert, delete, or modify a gene or gene sequences to silence, enhance, or otherwise change an organism's specific genetic characteristics.

Genetic engineering: Introduction of DNA, RNA or proteins manipulated by humans to effect a change in an organism's genome or epigenome.

Genetically modified: An organism whose genotype has been altered, including alteration by genetic engineering and non-genetic engineering methods.

Genome: The complete sequence of DNA in an organism.

Genotype: An individual's genetic identity.

Germ line: A cellular lineage in sexually reproducing organisms that produces the gametes (eggs and sperm) which transmit genetic material to the next generation.

Off-target effect: A direct, unintended, short- or long-term consequence of an intervention on an organism other than the intended effect on that organism.

Heterozygous: organism carries two different alleles for a certain gene.

Homologous recombination: is a type of genetic recombination in which nucleotide sequences are exchanged between two similar or identical molecules of DNA. It is most widely used by cells to accurately repair harmful breaks that occur on both strands of DNA, known as double-strand breaks.

Homozygous: organism carries two copies of the same allele for a certain gene.

Lateral gene transfer: The movement of genetic material between organisms other than via transmission from parent to offspring.

Wolbachia: A symbionts bacteria found in the cells of many invertebrates, including insects and nematodes that affect the reproductive biology of its hosts.

Wild type: A strain, gene, or characteristic which prevails among individuals in natural conditions, as distinct from an atypical mutant type.

ENDNOTES

[1] Sinkins and Gould, 'Gene drive systems for insect vectors' (2006) *Nature Reviews Genetics,* **7**, 427-435

[2] Austin Burt, 'Site-Specific Selfish Genes as Tools for the Control and Genetic Engineering of Natural Populations' (2003) *Proc. R. Soc. Lond. B,* **270,** 921-928

[3] Gantz, Valentino M., and Ethan Bier. "The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations." *Science*348, no. 6233 (2015): 442-444.

[4] Hammond *et al.*, 'A CRISPR-Cas9 Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector *Anopheles gambiae*' (2016), *Nature Biotechnology,* **34**, 78-83

[5] Akbari, Omar S., Hugo J. Bellen, Ethan Bier, Simon L. Bullock, Austin Burt, George M. Church, Kevin R. Cook et al. "Safeguarding gene drive experiments in the laboratory." *Science* 349, no. 6251 (2015): 927-929.

[6] Hoffmann, A. A., B. L. Montgomery, Jean Popovici, I. Iturbe-Ormaetxe, P. H. Johnson, F. Muzzi, M. Greenfield et al. "Successful establishment of Wolbachia in Aedes populations to suppress dengue transmission." *Nature*476, no. 7361 (2011): 454-457.

[7] Sinkins and Gould, 'Gene drive systems for insect vectors' (2006) *Nature Reviews Genetics,* **7**, 427-435

[8] Walker, Thomas, P. H. Johnson, L. A. Moreira, Inaki Iturbe-Ormaetxe, F. D. Frentiu, C. J. McMeniman, Yi San Leong et al. "The wMel Wolbachia strain blocks dengue and invades caged Aedes aegypti populations." *Nature* 476, no. 7361 (2011): 450-453.

[9] De Barro, Paul J., Brendan Murphy, Cassie C. Jansen, and Justine Murray. "The proposed release of the yellow fever mosquito, Aedes aegypti containing a naturally occurring strain of *Wolbachia pipientis*, a question of regulatory responsibility." *Journal für Verbraucherschutz und Lebensmittelsicherheit* 6, no. 1 (2011): 33-40.

[10] Gantz *et al*., 'Highly Efficient Cas9-Mediated Gene Drive for Population Modification of the Malaria Vector Mosquito *Anopheles stephensi*' (2015), Proceedings of the National Academy of Sciences, **112,** E6736–E6743

[11] Hammond *et al.*, 'A CRISPR-Cas9 Gene Drive System Targeting Female Reproduction in the Malaria Mosquito Vector *Anopheles gambiae*' (2016), *Nature Biotechnology,* **34**, 78-83

[12] Ibid.

[13] 'Merck Biopharma Cup Honours Young Scientists' *Merck News Release*. Published 26 July 2016, Accessed 5 October 2016, http://news.merck.de/N/0/41220CEBA361F903C1257FFB00693B4B/$File/InnovationCupPressRelease2016final.pdf

[14] Amy Harmon, 'Fighting Lyme Disease in the Genes of Nantucket's Mice' *The New York Times*. Published 7 June 2015, Accessed 5 October 2016, http://www.nytimes.com/2016/06/08/science/ticks-lyme-disease-mice-nantucket.html?_r=0

[15] The National Academies of Sciences, Engineering and Medicine, 'Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values' (National Academies Press, 2016).

[16] Ibid p51.

[17] Akbari, Omar S., Hugo J. Bellen, Ethan Bier, Simon L. Bullock, Austin Burt, George M. Church, Kevin R. Cook et al. "Safeguarding gene drive experiments in the laboratory." *Science* 349, no. 6251 (2015): 927-929.

[18] Esvelt et al., 'Concerning RNA-guided gene drives for the alteration of wild populations' (2014) eLife, 3, e03401. For a successful reversal drive in yeast see: DiCarlo et al., 'Safeguarding CRISPR-Cas9 Gene Drives in Yeast' (2015), Nature Biotechnology, 33, 1250-1255

[19] Esvelt et al., 'Concerning RNA-guided gene drives for the alteration of wild populations' (2014) eLife, 3, e03401

[20] Noble et al, 'Daisy-chain gene drives for the alteration of local populations' *bioRxiv,* Published 7 June 2016, Accessed 5 October 2016, http://biorxiv.org/content/early/2016/06/06/057307

[21] Kevin Esvelt, 'Daisy Drives Systems' *Sculpting Evolution,* Accessed 5 October 2016, http://www.sculptingevolution.org/daisydrives

[22] Genetically Modified Organisms (Contained Use) Regulations 2014, sch 2 pt 1.

[23] Contained use of GMOs refers to "any activity involving GMOs where barriers are used to limit contact with and protect humans and the environment", this includes e.g. laboratory work with GMOs (HSE, The Genetically Modified Organisms (Contained Use) Regulations 2014: Guidance on Regulations).

[24] In Directive 2001/18/EC, these are also referred to as 'placing on the market' and 'other purpose than placing on the market'.

[25] Annex III, Directive 2009/41/EC.

[26] Annex III, Directive 2009/41/EC.

[27] Annex II, Directive 2001/18/EC.

[28] The HSE and the Secretary of State for Environment, Food and Rural Affairs form the competent authority for the Contained Use Regulations in England and Wales.

[29] The SACGM is a non-statutory advisory body, providing advice to the HSE and DEFRA Ministers relating to contained uses of GMOs.

[30] HSE, The SACGM Compendium of Guidance – Part 5: Genetic Modification of Animals.

[31] Similar points were raised in the February 2016 Gene Drives Policy Report of the Netherlands National Institute of Public Health and the Environment.

[32] HSE, The SACGM Compendium, Part 5, p.10.

[33] HSE, The SACGM Compendium, Part 5, p.19.

[34] HSE, Guidance on Regulations, p.23.

[35] Key points are covered in Chapter 4: Regulation of GM insect technologies of the House of Lords Science and Technology Committee's Genetically Modified Insects report.

[36] Discussed in paragraphs 92-96 of the House of Lords Genetically Modified Insects report.

[37] Through its Subsidiary Body on Scientific, Technical and Technological Advice.

[38] Available through http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/.

[39] OIE, Terrestrial Animal Health Code, Chapter 1.5.

[40] OIE, Guidelines for Assessing the Risk of Non-Native Animals Becoming Invasive.

[41] OIE, Terrestrial Manual, Chapter 1.1.4.

[42] Adopted from, The National Academies of Sciences, Engineering and Medicine, 'Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values' (National Academies Press, 2016) ch 12.