Section 6

Environment

Section 6 – The natural environment

Outline

Human interventions increasingly have an impact on the biosphere. This chapter considers the potential ecological implications of deliberate or accidental releases of genome-edited organisms into the wild.

Three increasingly ambitious uses of genome technologies are discussed: genetically modified mosquitoes, bred to reduce the population of mosquitoes capable of acting as vectors of human disease, the elimination of non-indigenous predators to restore a national ecosystem and the revival and possible reintroduction of extinct species.

The concept of a 'gene drive' is introduced and its mechanism of action described in comparison to the propagation of genes through Mendelian inheritance and the fixation of variants in a sexually reproducing population by Darwinian evolution. Applications of gene drive technology are identified, including eradication of insect pests and disease vectors, reduction of invasive species and management of ecosystems.

The significant advantages of combining gene drive technology with the CRISPR-Cas9 genome editing system is described. Work to develop a low-cost, self-sustaining gene drive technology to control malaria-transmitting mosquito populations is described. Different possible refinements to the gene drive technique in order to improve the level of control, or to reduce or redress adverse outcomes are elaborated.

International, regional and some domestic legal and regulatory measures relating to the release into the wild of genetically altered organisms are noted. These include the Convention on Biological Diversity and its Cartagena and Nagoya protocols, and various regulatory measures in the EU, UK and US, as well as international guidance. Ambiguities and limitations of these instruments are suggested.

The nature of the moral and societal considerations relating to releases of genetically altered organisms into the wild is noted, and a number of considerations are discussed, including the importance of respect for the natural world and the sensitivity of natural ecologies, concern for the welfare of animals, risk of unpredictable ecosystem effects and ecological catastrophe. Responses to uncertainty, and the involvement of a broader engagement of a range of interests, actors and knowledge forms in precautionary approaches is considered. The prospects of reversing the effects of gene drives are examined and issues of technology transfer between rich and poor countries, and global justice are discussed. The need for responsible innovation approaches is highlighted.

Introduction

6.1 An important consideration for bioethics, at least since the appearance of genetic engineering, has been the environmental impact of human interventions. Human population requirements for food, energy and natural resources have changed the natural environment substantially, as have the outputs of industrial processes.[329] These effects have been so profound that many commentators and working scientists have adopted a way of referring to them as characterising a new aeon in geological time, the Anthropocene.[330] The environmental effects of human activity in general, including some of the consequences of biotechnology are, nevertheless, usually unintended or unavoidable by-products of the pursuit of a principal purpose such as agriculture and, as such, are usually counted on the 'risk' side of the balance sheet.

[329] References to the 'natural environment' are to the physical conditions that constitute the habitat for living things. The natural environment comprises distinguishable ecosystems regulated by processes that do not involve substantial human intervention, as well as relatively unbounded resources such as air and water. It is distinguished from conditions that have been fundamentally transformed by and are regulated by human activity (such as urban and agricultural areas). Ecosystems within the natural environment may be highly integrated (with high interdependency between elements) and dynamically stable over time. Because they are not in equilibrium, a disturbance (such as the introduction of a new microorganism, plant or animal species) may destabilise the ecosystem in a way that adversely affects the survival of certain organisms or produces conditions for other organisms to thrive, changing the composition of an ecosystem.

[330] This may be dated from the mid-20th century, from the industrial revolution in the late 18th century or even from the agricultural revolution in the Neolithic era depending on what evidence (for example, from the atmosphere or lithosphere) is adduced. The Stratigraphy Commission of the Geological Society of London has been considering a proposal to make the Anthropocene a formal division of geological time since 2009. The Guardian (29 August 2016) *The Anthropocene epoch: scientists declare dawn of human-influenced age*, available at: https://www.theguardian.com/environment/2016/aug/29/declare-anthropocene-epoch-experts-urge-geological-congress-human-impact-earth. See also http://anthropocene.info/.

6.2 We have previously (in sections 4 and 5) noted the risks of environmental contamination and the various biosafety measures that may be taken to avoid direct damage to the environment or to people as a result of uncontrolled exposure to, or release of, genome-edited organisms; we shall return to these in the section 7. In the present section we will consider the potential uses and environmental implications of genome editing, beyond 'contained' applications in research, medicine and industry, and managed cultivation and breeding in agriculture. The subject is therefore organisms that are intended for release into the wild (including those that are released deliberately to change the conditions of an existing ecosystem), their effects on animals, plants and microorganisms in the wild and the implications of these effects on human interests.

6.3 The uncontrolled impact of biotechnology on the environment may broadly abide by similar constraints and pressures that produce Darwinian evolution, speciation and extinction.[331] In section 5, we observed, in the context of agricultural biotechnology, how domesticated – especially highly engineered – organisms that appear to function well in the controlled, artificial environments for which they are bred (such as intensive agricultural systems with high fertiliser inputs, protected by herbicides and pesticides), are typically less well adapted than wild varieties to conditions outside these controlled environments (lacking immunological robustness, for example). Without the artificial inputs to which they are adapted, which form their particular environmental niche, domesticated organisms tend to fail to thrive and are out-competed by wild types. The concern has long existed, however, that a newly introduced organism, in certain conducive conditions, could take root and tip its surrounding ecosystem into a possibly unpredictable new state.[332]

6.4 Notwithstanding the large-scale risks of environmental impacts, if the use of biotechnology in general, and genome editing in particular, has the potential to produce large-scale systemic change it also raises the possibility of deliberately altering environmental conditions for a range of arguably beneficial purposes, including improved human and animal health, economic convenience, and even environmental geoengineering.[333] This may have the effect of making hitherto insuperable environmental constraints more tractable to human control, altering the range of achievable future states. In this section we look at the potential uses of genome editing of organisms for release into the wild, which may go on to grow and propagate naturally, before looking at a powerful use of genome editing in combination with 'gene drive' technology, which can cause the altered genotype to spread rapidly through a sexually reproducing wild population, by ensuring that it is inherited preferentially.

Use of genome technologies in the wild

6.5 Ecosystems are integrated open systems constantly subject to perturbation. Pests and diseases that may be remote or suppressed may spread and become epidemic, sometimes precipitously, as a result of the introduction of novel organisms or subtle changes in conditions.[334] One potential application of genome editing is effectively to arm a particular species in the continuous struggle between organisms. This might be accomplished by providing a selective advantage to that particular species, such as resistance to endemic disease.

[331] On extinction see Raup DM (1994) The role of extinction in evolution *Proceedings of the National Academy of Sciences* **91**(15): 6758-63.
[332] Doody JS, Soanes R, Castellano CM, *et al*. (2015) Invasive toads shift predator-prey densities in animal communities by removing top predators *Ecology* **96**(6): 2544-54.
[333] Royal Society (2009) *Geoengineering the climate: science, governance and uncertainty*, available at: https://royalsociety.org/~/media/Royal_Society_Content/policy/publications/2009/8693.pdf.
[334] Goldfarb B (2016) A virus is taming Australia's bunny menace, and giving endangered species new life *Science News*, doi: 10.1126/science.aaf4075 (published 17 February 2016).

6.6 Although mechanisms by which traits spread through a population may be understood at a theoretical level, their transmission is difficult to predict in complex, concrete circumstances.[335] While environmental release of organisms that are designated as 'genetically modified' is legally controlled (see below), the challenge of preventing such organisms from destabilising an ecosystem is probably usually not as great as the challenge of producing a modified phenotype capable of surviving as well as a wild variety and establishing itself in an uncontrolled environment.[336] Nevertheless, a number of high ambition initiatives using genome technologies have been proposed and developed with the aim of altering the characteristics of a breeding population of animals or altering the characteristics of the ecosystem of which they are a part.

6.7 An area in which research and innovation is advancing rapidly is the release of genetically modified insects. Oxitec Ltd, a company that started as a spin-out from academic research in the UK, has developed a genetically modified *Aedes aegypti* mosquito (the OX513A mosquito) using GM technology (i.e. not genome editing systems).[337] The *Aedes aegypti* is a vector of dengue fever in South America; Oxitec's focus is controlling the mosquito population, and therefore the likelihood of disease transmission, by breeding mosquitoes in which essential gene expression is inhibited, leading to cell death and the death of the insect before it reaches maturity.[338] Following trials in Grand Cayman, Brazil and Panama, the OX513A has received approval for use in Brazil where Oxitec has established a factory to scale up production.[339] The company has also applied the same technology to control agricultural pests, and has received approval for open field trials in Brazil and the USA for genetically modified Mediterranean fruit flies and Diamondback moths, which are the major pest affecting brassica crops.[340]

6.8 Another high ambition project potentially drawing on genome technologies was announced by the New Zealand government in July 2016. The aims of the project, under the rubric 'Predator Free New Zealand' are to eliminate ground-dwelling predators from the archipelago.[341] The public-private project will be started with NZ$28 million (£15.5 million) seed funding to explore a number of strategies targeted to the main non-indigenous predators (rats, weasels and possums). The strategies to be explored include the use of a 'Trojan Female Technique' (based on the

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[335] "While we can test for the safety and nutrient values of food plants, we do not possess the capacity for extensive testing of the behaviour of every genetic variant in a natural ecosystem", response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

[336] This comment refers to the technical challenge only – it should not be taken to imply that it is unnecessary to be concerned about the possibility of catastrophic contamination.

[337] Oxitec Ltd. is a spin-out from Oxford University's Department of Zoology, acquired by Intrexon Corporation in 2015. It is pursuing similar aims to those of Target Malaria (see below) through a private enterprise business model. See: http://www.ox.ac.uk/news/2015-08-10-biotech-spin-out-be-sold-160-million-0.

[338] The effect can, in principle, be prevented by introducing an antibiotic – tetracycline – to the water in which the larvae feed allowing the larvae to survive and reproduce. Curtis Z, Matzen K, Neira Oviedo M, *et al*. (2015) Assessment of the impact of potential tetracycline exposure on the phenotype of *Aedes aegypti* OX513A: implications for field use *PLoS Neglected Tropical Diseases* **9**(8): e0003999.

[339] MIT Technology Review (17 February 2016) *Inside the mosquito factory that could stop dengue and Zika*, available at: https://www.technologyreview.com/s/600821/inside-the-mosquito-factory-that-could-stop-dengue-and-zika/. In April 2016 Anvisa, the Brazillian Health Regulatory Agency, granted Oxitec a special temporary registration authorising the research use of OX513A across Brazil. Under the conditions set by Anvisa, Oxitec and any public authority sponsoring the use of GM mosquitoes are still obliged to monitor all releases and to submit data to Anvisa on a regular basis. (See: http://portal.anvisa.gov.br/noticias/-/asset_publisher/FXrpx9qY7FbU/content/anvisa-decide-que-mosquito-transgenico-e-objeto-de-regulacao-sanitaria/219201/pop_up?_101_INSTANCE_FXrpx9qY7FbU_viewMode=print&_101_INSTANCE_FXrpx9qY7FbU_languageId=en_US).

[340] Waltz E (2015) Oxitec trials GM sterile moth to combat agricultural infestations *Nature Biotechnology* **33**(8): 792-3. APHIS, Environmental Assessment for the environmental release permit application for Oxitec diamondback moth strains, available at: http://www.aphis.usda.gov/brs/aphisdocs/13_297102r_fonsi.pdf; Approval document for the Mediterranean fruit fly in Brazil: http://www.jusbrasil.com.br/diarios/69287490/dou-secao-1-23-04-2014-pg-51. See also: http://www.oxitec.com/agriculture/our-products/medfly/ and http://www.oxitec.com/agriculture/our-products/diamond-back-moth/.

[341] See http://predatorfreenz.org/; BBC news (25 July 2016) *New Zealand aims to become predator-free by 2050*, available at: http://www.bbc.co.uk/news/blogs-news-from-elsewhere-36883799.

introduction of females carrying mutated mitochondrial DNA that leads to the production of male offspring with impaired sperm function).[342]

6.9 A more speculative use of genome technologies is to reconstruct and reintroduce extinct species from the genome upwards. Revive and Restore, a company funded with Silicon Valley venture capital, promises 'genetic rescue for endangered and extinct species', and has a 20-year roadmap to bring back extinct species like the passenger pigeon and the heath hen, as well as more exotic ambitions like the woolly mammoth.[343] This latter may be a fanciful, if headline-grabbing suggestion: it would be necessary to rebuild genomes from archaic samples discovered in permafrost; furthermore, almost nothing is known about mammoth reproduction, and there is little expertise in artificial fertilisation of elephant eggs (which may be required) and *in vitro* culture of elephant embryos. A more technically plausible possibility, however, although one that is far more ethically complex, is the revival of archaic humans such as *Homo neanderthalensis*, using synthetic biology and existing cell reconstruction and culture techniques.[344]

Gene drive

6.10 Existing wild varieties tend to be best adapted to their environment and, all other things being equal, the spread of a trait through a naturally reproducing population is favoured only when the trait has a selective advantage (which human intervention provides, in effect, for agriculturally valuable organisms).[345] Researchers have discovered a way to accelerate the population-wide propagation of a trait by using a technique called a 'gene drive'.[346]

6.11 In most cases the prevalence of a gene variant in a population can be adequately explained by natural selection, whereby a relatively successful variant provides the organism with a competitive advantage so that organisms carrying that variant reproduce more (and *vice versa* for relatively unsuccessful variants). Thus, a beneficial variant can be expected to increase in prevalence in a population despite the fact that it is inherited through exactly the same mechanism of genetic recombination as a less beneficial (or even a harmful) variant. There are cases, however, in which the higher prevalence is explained not by the relatively high survival rate of the organisms carrying the gene variant but by preferential inheritance of specific variants through 'intragenomic conflict'.[347] Gene drive systems promote the spread of genetic elements through populations by ensuring they are inherited more frequently than by Mendelian inheritance would predict. This

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[342] Gemmell NJ, Jalilzadeh A, Didham RK, Soboleva T and Tompkins DM (2013) The Trojan female technique: a novel, effective and humane approach for pest population control *Proceedings of the Royal Society B: Biological Sciences* **280**(1773): 20132549.

[343] See http://reviverestore.org/. Cf. Shapiro B (2015) Mammoth 2.0: will genome engineering resurrect extinct species? *Genome Biology* **16**(1): 228.

[344] In 2013 it was misreported that Harvard geneticist George Church was seeking a human surrogate mother to assist with experiments to produce a Neanderthal baby. Although the story turned out to be false, the proposal is more technically feasible than the revival of many other species that have been suggested. See: http://www.bostonherald.com/news_opinion/local_coverage/2013/01/harvard_professor_blasts_neanderthal_clone_baby_rumor_web.

[345] A textbook example is the adaptation of the British peppered moth, from pale to dark, as a result of the blackening of its habitat by coal pollution in the early nineteenth century. The underlying genetic mutation has recently been identified as a transposable element (see box 6.1): Van't Hof AE, Campagne P, Rigden DJ, *et al*. (2016) The industrial melanism mutation in British peppered moths is a transposable element *Nature* **534**(7605):102-5.

[346] For a thoroughgoing examination of the uses of gene drive and questions arising, see National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and. The overarching conclusion of this report is that "There is insufficient evidence available at this time to support the release of gene-drive modified organisms into the environment. However, the potential benefits of gene drives for basic and applied research are significant and justify proceeding with laboratory research and highly-controlled field trials."

[347] Intragenomic conflict occurs when particular allele or gene variant within a genome is preferentially inherited at the expense of other variants, with selection occurring through a mechanism operating at the level of the cellular reproduction rather than at the level of the organism. Spencer HG (2003) Intragenomic conflict *Encyclopedia of Life Sciences*, doi: 10.1038/npg.els.0001714. See also: Burt A and Trivers R (2008) *Genes in conflict: the biology of selfish genetic elements* (Cambridge, MA: Harvard University Press).

allows a genetic variant to spread through a population even though it does not provide a selective advantage to the organism. In particular, so-called autocatalytic homing endonucleases are commonly referred to as 'gene drives'[348]

6.12 The concept of a 'gene drive' was coined by Christopher Curtis at the London School of Hygiene and Tropical Medicine in 1968, who proposed using translocations (rearrangements of genetic material) to drive anti-pathogenic genes into wild vector species.[349] It remained theoretical, however, until Austin Burt and colleagues at Imperial College, London, demonstrated that such a nuclease-based gene drive functions in an animal (the mosquito *Anopheles gambiae*) in 2011.[350] Gene drives aim at population, species or ecosystem-level genetic engineering. There are natural and synthetic gene drive systems.[351] Synthetic drives are being explored to understand how populations might be altered through adding, disrupting, or editing genes, or by propagating traits that influence fitness or reproductive capacity.

Box 6.1: Gene drive systems

Natural gene drives were recognised in the middle of the last century in various species.[352] For example, in *Drosophila* (a small fly) the *segregation distorter* (*sd*) locus ensures that one of two alleles is preferentially transmitted to offspring, a phenomenon known as meiotic drive, whereas typical parental alleles have a 50% chance of being inherited. Segregation distorters occur in other species, such as *sk* in the mould *Neurospora* spp and the mouse *t*-haplotype. Transposable elements (TEs), sometimes referred to as 'jumping genes' may also be thought of as natural gene drives: they are DNA segments able to move from one location to another (transposition), sometimes with replication, and independently of selection. Transposable elements are widespread throughout nature (they are present in bacteria, plants and animals) and are exemplified by a class of transposable elements in *Drosophila* called P elements, which originated in the mid-twentieth century and have since spread through all *Drosophila* populations.[353]

In general, transposition is catalysed by a transposase enzyme encoded by the transposable element; transposase has some functional parallels with homing endonucleases, which also catalyse natural gene drives. Homing endonucleases are enzymes that recognise and cut rare (in the range of tens of base pairs) DNA sequences. Because the recognition cut site in a naïve DNA sequence matches sequences on either side of the homing endonuclease gene (HEG), repair of the cut results in a copy of the homing endonuclease gene being copied into the cut site – a process termed 'homing'. This means that in diploid cells (cells that have two copies of each chromosome), where one copy of a chromosome contains a homing endonuclease gene and one does not, the naïve chromosome may acquire a copy independently of selection. These classes of genes or genetic elements may all be considered natural gene drives because they facilitate their own perpetuation with little dependence on conferring a selective advantage

Applications of gene drive technology

6.13 Gene drives have thus far found no application in the production of domesticated plant varieties as breeding is highly controlled anyway. They might, however, be useful in controlling plant pathogens, or to control pests and weeds by reversing pesticide or herbicide resistance.[354] They also have promise as methods for control or eradication of insect pests and vectors of disease directly, including diseases affecting livestock and humans.[355] These include many insect-borne tropical diseases, such as dengue, malaria and Zika. Applications that have been suggested include the reduction or elimination of invasive (or otherwise undesired) species such as cane

[348] Gantz VM and Bier E (2015) The mutagenic chain reaction: a method for converting heterozygous to homozygous mutations *Science* **348**(6233): 442-4.
[349] Curtis CF (1968) Possible use of translocations to fix desirable genes in insect pest populations *Nature* **218**(5139): 368-9.
[350] Burt A (2003) Site-specific selfish genes as tools for the control and genetic engineering of natural populations *Proceedings of the Royal Society of London Series B: Biological Sciences* **270**(1518): 921-8; Windbichler N, Menichelli M, Papathanos PA, *et al*. (2011) A synthetic homing endonuclease-based gene drive system in the human malaria mosquito *Nature* **473**(7346): 212-5.
[351] Sinkins SP and Gould F (2006) Gene drive systems for insect disease vectors *Nature Reviews Genetics* **7**(6): 427-35.
[352] Response to *Call for Evidence* by Target Malaria.
[353] Spradling AC, Bellen HJ and Hoskins RA (2011) Drosophila P elements preferentially transpose to replication origins *Proceedings of the National Academy of Sciences* **108**(38): 15948-53.
[354] Response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre; BBSRC and MRC.
[355] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

toads, lionfish, giant African snail, kudzu, black rat and zebra mussels.[356] This might in principle be achieved using gene drive by altering sex ratio, reducing fertility, or producing chemical sensitivity.[357] In the future, gene drive systems could be introduced into vectors of livestock and plant disease, so that they are no longer able to transmit specific pathogens.[358] In addition, it may be possible for gene drive systems to be used to accelerate the propagation of traits within mammalian genomes, for example to disseminate disease resistance within a breed of pigs.[359] Ultimately, gene drive systems could expedite the expression of human preferences over the composition of the biosphere.

6.14 Among the most promising and well advanced applications of gene drive systems are those targeting wild insect populations that transmit tropical diseases that affect human populations. It has been proposed that synthetic gene drives could be released to control mosquito populations or their ability to transmit malaria, dengue fever, yellow fever and Zika.[360] Strategies for the use of gene drive systems include making the insect vectors that would otherwise carry them refractory to disease-causing parasites and altering the sex ratio in favour of males (because only female mosquitoes bite).[361] For example, the Target Malaria research consortium aims, by using a gene drive system, to inactivate specific genes in two species of *Anopheles* malaria-transmitting mosquitoes, *Anopheles gambiae* and *Anopheles arabiensis*.[362] (Worldwide there are approximately 3,500 mosquito species, although only about 40 *Anopheles* species are able to transmit malaria in a way that presents a substantial risk to human health.)

Converging technologies: CRISPR-enabled gene drive

6.15 The convergence of gene drive systems with the CRISPR-Cas9 genome editing system to effect specifically targeted genomic modifications has been described as a 'game changer' in the field.[363] Gene drive systems that harness CRISPR-Cas9 have been applied in research on different organisms including mosquitoes and yeast.[364] In April 2015, a US group reported a very efficient gene drive system for *Drosophila* which is capable of driving a mutation into 97% of offspring in just two generations.[365] In this system, the gRNA, the edited (desired) version of the target gene

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[356] Webber BL, Raghu S and Edwards OR (2015) Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *Proceedings of the National Academy of Sciences* **112**(34): 10565-7; Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[357] Webber BL, Raghu S and Edwards OR (2015) Is CRISPR-based gene drive a biocontrol silver bullet or global conservation threat? *Proceedings of the National Academy of Sciences* **112**(34): 10565-7.

[358] Alphey L and Alphey N (2014) Five things to know about genetically modified (GM) insects for vector control *PLoS Pathogens* **10**: e1003909, available at: http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003909.

[359] Professor Bruce Whitelaw, personal communication, September 2016.

[360] See Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401; Carvalho DO, McKemey AR, Garziera L, *et al*. (2015) Suppression of a field population of Aedes aegypti in Brazil by sustained release of transgenic male mosquitoes *PLoS Neglected Tropical Diseases* **9**(7): e0003864, available at: http://journals.plos.org/plosntds/article?id=10.1371/journal.pntd.0003864; Alphey L and Alphey N (2014) Five things to know about genetically modified (GM) insects for vector control *PLoS Pathogens* **10**: e1003909, available at: http://journals.plos.org/plospathogens/article?id=10.1371/journal.ppat.1003909; National Academies of Sciences, Engineering, and Medicine (2016) Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

[361] See for example: Galizi R, Doyle LA, Menichelli M, *et al*. (2014) A synthetic sex ratio distortion system for the control of the human malaria mosquito *Nature Communications* **5**: 3977.

[362] Target Malaria grew out of a university-based research programme and remains a non-profit initiative, funded by a core grant from the Foundation for the National Institutes of Health (FNIH) through a programme of the Bill & Melinda Gates Foundation. Participating laboratories receive additional funding from a variety of additional sources. See: http://targetmalaria.org/who-we-are/.

[363] Ledford H (2015) CRISPR, the disruptor *Nature* **522**(7554): 20-4.

[364] Gantz VM, Jasinskiene N, Tatarenkova O, *et al*. (2015) Highly efficient Cas9-mediated gene drive for population modification of the malaria vector mosquito Anopheles stephensi *Proceedings of the National Academy of Sciences*, doi: 10.1073/pnas.1521077112 (published online 23 November 2015); DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5.

[365] Gantz VM and Bier E (2015) The mutagenic chain reaction: A method for converting heterozygous to homozygous mutations *Science* **348**(6233): 442-4.

and Cas9 endonuclease are combined into a cassette (denoted 'GDC' in the diagram in box 6.2), so that Cas9 and the gene modification are inserted together into the target gene. Such a cassette has the potential to create a self-sustaining gene drive, a process that has been described as a 'mutagenic chain reaction'.[366]

Box 6.2: CRISPR-enabled gene drive

BoxText style An experimental use of a CRISPR-Cas9 enabled gene drive in *Drosophila* involved a gene modification that had been introduced on one chromosome copying itself onto the unmodified sister chromosome.[367] This mechanism ensured that during the process by which the gametes (sperm or egg) are produced, every gamete genome harboured a copy of the gene drive. This meant that when the flies bred with wild animals lacking the gene drive element, they passed it on to the resultant 1-cell embryo. In the 1-cell embryo, the gene drive mechanism rapidly recapitulates; the gene drive copies itself onto the naïve chromosome inherited from the wild animal so that now both corresponding chromosomes contain the drive. Normal DNA replication and cell division subsequently ensures that all cells of the embryo and ultimately the adult contain the gene drive.

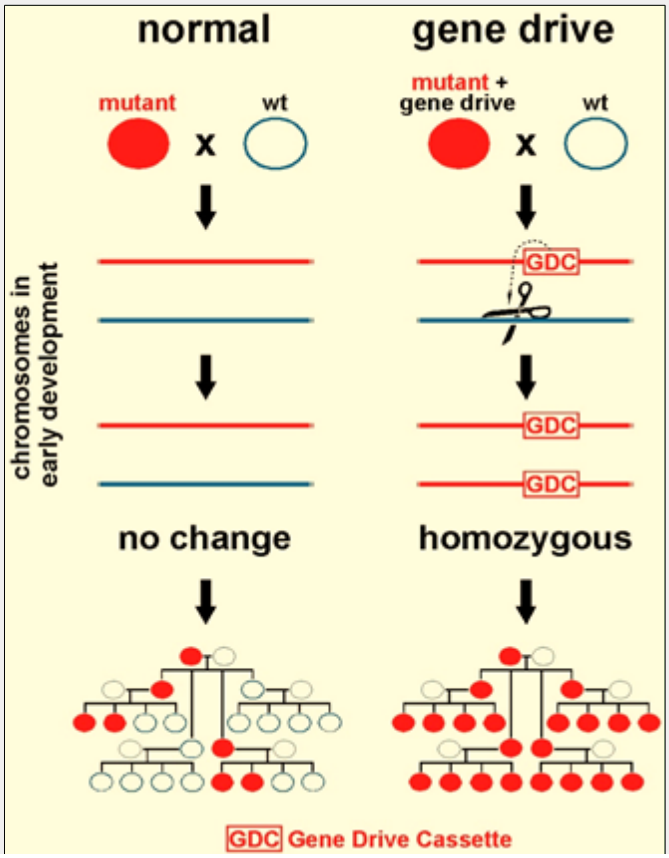

Illustration provided by Dr Tony Perry, member of the Working Group.

6.16 Strategies currently under investigation involve protein engineering endonucleases to act in a similar way to homing endonucleases discussed above These would disrupt essential genes such as genes involved in reproduction (so as to reduce fertility or unbalance the sex ratio in favour of males) or genes that are required for pathogen transmission.[368] The CRISPR-Cas9 system offers transformative potential in this context because until its arrival there had been no effective system for specific gene knockout in mosquitoes.[369] The Target Malaria research is currently targeted to sub-Saharan Africa where around 90% of all malaria-related deaths occur (currently Burkina Faso,

[366] Ibid.
[367] Ibid.
[368] Response to *Call for Evidence* by Target Malaria; see also http://targetmalaria.org/.
[369] Evidence from fact-finding meeting on animal research.

Mali and Uganda). Adoption of the CRISPR-Cas9 system has made gene drive potentially more accessible and relatively easier to apply than previous methods, which would provide a low-cost, self-sustaining technology, that could transform the mosquito population over epidemiologically relevant time and region. This is critical in a context where resources to fight the disease are severely limited, making it unfeasible to rear sufficient numbers of modified mosquitoes that would be required for an inundative approach.[370] It has a potential added advantage of reducing dependence on environmentally harmful insecticides and freeing low resource health care systems from having to provide anti-malarials or buy immunisations. Target Malaria envisage deployment within five to 10 years (from 2016) to allow safety and efficacy testing and risk assessment but – assuming all goes well in the interim – it is likely to be longer that this before they can begin to make a difference in practice.

Refinements for control of gene drives

6.17 Gene drives have a number of limitations. Because they depend on the natural cycle of sexual reproduction in the target organism, the pace of diffusion is limited. They are therefore most effective in fast-reproducing species, such as insects, and in simple genetic systems. Furthermore, gene drives cannot escape evolution, so the gene drive components or other features of the host organisms may mutate and these mutations enter into evolutionary selection. Non-homologous end joining tends not to preserve sequences at the break termini; and gene drive function would need to be controlled because of DNA damage and immune processes that are only partly understood.[371] Modelling the effects of gene drive systems in the wild is a complex problem and appropriate risk assessment and modelling tools will need to be developed for each set of circumstances. These will need to establish to what extent gene drives are likely to be prescriptive in the wild. To the extent that a given drive cannot be prescriptive (and yet the perceived benefits outweigh the attendant risks) mitigation strategies will have to take into account the ecological impact of the drive, which might make it impossible to restore the initial conditions of the system. The relative power of gene drive and natural selection is a subject of current investigation and discussion including a recent substantial report by the US National Academies of Science, Engineering, and Medicine.[372]

6.18 A number of refinements have been proposed and developed to gene drive technologies strategies to address the potential risks of uncontrolled proliferation of self-sustaining gene drives in wild populations.[373] '**Reversal drives**' could be deployed to overwrite changes introduced by an initial drive.[374] '**Immunizing drives**' could be introduced to block the spread of unwanted gene drives by pre-emptively or reactively altering target sequences so that they would not be recognised by the first drive. '**Precision drives**' could be more finely constrained to particular species or subpopulations by targeting sequences unique to those groups so as to reduce the possibility of transmission between (closely-related) species. Using two drives, the first to alter a defined population to provide a unique target and the second to make the desired phenotypic alteration could help to ensure that the second drive does not leave a controlled population, such as an island habitat.

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[370] See paragraph 6.7 above.

[371] Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[372] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and See also: DeFrancesco L (2015) Gene drive overdrive *Nature Biotechnology* **33**(10): 1019-21; Unckless RL, Clark AG and Messer PW (2016) Evolution of resistance against CRISPR/Cas9 gene drive *bioRxiv*, doi: 10.1101/058438 (posted online 11 June 2016).

[373] Some of these risks and benefits, and a typology of refinements to enhance safety, are outlined by Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[374] This would leave only the guide RNAs and the gene encoding Cas9 as evidence of past editing; see Esvelt et al. 2014 (op. cit.). It could not, however, reverse any ecological effects of the initial drives that had taken place in the interim.

6.19 Other strategies might limit the population suppression effects of releasing a gene drive system, avoiding species extinction and ecological risk. '**Sensitizing drives**' might make a target organism sensitive to environmental chemicals. These could work in different ways, for example, by reversing known mutations that confer resistance to pesticides or herbicides, by introducing an enzyme that would metabolise an environmentally neutral compound into toxin within the organism, or by swapping a conserved gene for a version that is strongly inhibited by a particular small molecule. 'Evolutionarily unstable drives' could also be used, whereby reproductive genes carried by a standard drive on an autosome (i.e. not on a sex chromosome) would suppress the target population but natural selection would select against this loss of function within the population. Maintaining the effect of the initial drive would therefore require periodic release of the modified type.[375]

6.20 Population suppression could also be controlled by releasing '**interacting drives**', which would only cause the effect when the two drives encounter each other through mating. Finer control could be achieved by further releases of one or other of the drives to suppress one or other of the two genotypes or induced new species.[376] '**Split gene drives**', in which biallelic mutations introduced with an sgRNA-only transgene cassette can spread only when combined with an unlinked Cas9-only transgene cassette, are currently considered to have the greatest potential safety. This allows homozygous individuals lacking the Cas9 transgene to be isolated easily in subsequent generations.[377] The split system has been developed in brewer's yeast (*Saccharomyces cerevisiae*), in which it was shown to be as efficient as a gene drive construct encoding both Cas9 and sgRNA together.[378]

Law and regulation

6.21 Given the potential ecological consequences of the environmental release of genetically altered organisms a multi-layered regulatory system exists to govern this area of application. The International Convention on Biological Diversity (CBD) entered into force on 29 December 1993.[379] It has three main objectives: (1) The conservation of biological diversity, (2) The sustainable use of the components of biological diversity, and (3) The fair and equitable sharing of the benefits arising out of the utilization of genetic resource. Article 8(g) calls on Contracting Parties to "Establish or maintain means to regulate, manage or control the risks associated with the use and release of living modified organisms resulting from biotechnology which are likely to have adverse environmental impacts that could affect the conservation and sustainable use of biological diversity, taking also into account the risks to human health".[380] Art.19(2) calls on Contracting Parties to "take all practicable measures to promote and advance priority access on a fair and equitable basis by Contracting Parties, especially developing countries, to the results and benefits arising from biotechnologies based upon genetic resources provided by those Contracting Parties […] on mutually agreed terms."

6.22 The *Cartagena Protocol on Biosafety* is an international agreement that aims to ensure the safe handling, transport and use of living modified organisms (LMOs) resulting from modern biotechnology that may have adverse effects on biological diversity, taking also into account risks

[375] Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.
[376] Ibid.
[377] DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5.
[378] DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5; Akbari OS, Bellen HJ, Bier E, *et al*. (2015) Safeguarding gene drive experiments in the laboratory *Science* **349**(6251): 927-9.
[379] See: https://www.cbd.int/convention/text/.
[380] Synthetic biology is not explicitly addressed in the CBD or its protocols. However, Decision XII/24, of the Conference of Parties to the CBD encourages the use of precautionary approach in respect of organisms, components and products resulting from synthetic biology. It also establishes an Ad Hoc Technical Expert Group to, inter alia, review the sufficiency of existing provisions, including consideration of the applicability of the Cartagena Protocol, examining the similarities and differences between living modified organisms (as defined in the Protocol) and organisms, components and products of synthetic biology techniques, and to develop an operational definition of synthetic biology. (See: https://bch.cbd.int/synbio)

to human health.[381] It gives effect to the 'precautionary approach' set out in Principle 15 of the *Rio Declaration on Environment and Development*.[382] Parties to the Protocol must ensure, among other things, that release of any living modified organism is undertaken in a manner that prevents or reduces the risks to biological diversity, also taking into account risks to human health. It was adopted by the Conference of the Parties to the Convention on 29 January 2000 and entered into force on 11 September 2003.[383]

6.23 The *Nagoya Protocol on Access to Genetic Resources and the Fair and Equitable Sharing of Benefits Arising from their Utilization* is an agreement that aims at sharing the benefits arising from the utilisation of genetic resources in a fair and equitable way.[384] It entered into force on 12 October 2014. It is based on the principle (Article 5) that equitable returns should be made for the provision of genetic resources by donor countries (i.e. non-exploitation of one party by another, rather than global solidarity). Article 8(b) calls on Parties to "Pay due regard to cases of present or imminent emergencies that threaten or damage human, animal or plant health, as determined nationally or internationally. Parties may take into consideration the need for expeditious access to genetic resources and expeditious fair and equitable sharing of benefits arising out of the use of such genetic resources, including access to affordable treatments by those in need, especially in developing countries." Article 23 has text relevant to technology transfer between countries but in relation to the achievement of the objective of the protocol (set out in Article 1) – which is about equitable benefit sharing contributing to the conservation of biological diversity and the sustainable use of its components (*i.e.* not about global health and technology transfer).[385] The CBD and protocols are implemented via European Union Law (including a directly applicable Regulation on in the Nagoya Protocol) and transposed through various pieces of domestic legislation in the UK under the responsibility of the Department of the Environment, Food and Rural Affairs (Defra) and its agencies (and corresponding bodies in the home countries).[386]

6.24 Regional and national legislation exists in different areas relating to the environmental release of modified organisms. For example, in the EU, this is governed by Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms (GMOs). This contains a definition of GMOs that applies also to plants, although the applicability of this definition to organisms altered using genome editing techniques is currently (in August 2016) contested.[387] In the US (which is not a signatory to the *Cartagena Protocol*) biotechnology products that have potential environmental impacts are covered by the National Environmental Policy Act of 1969 and presumed to be subject to the 1986 Coordinated Framework for the Regulation of Biotechnology, under the combined aegis of the Food and Drug Administration, US Department of Agriculture and Environmental Protection Agency. The Centers for Disease Control and Prevention also has regulatory competence where the product involves a threat to public health.[388] The Co-ordinated Framework is currently under review and there is potential inconsistency with regard to which agency has the responsibility and capacity to regulate gene drive, genome-edited and genetically modified animals.[389] This was highlighted by the fact that Oxitec's genetic

[381] See: https://bch.cbd.int/protocol.
[382] "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." See: http://www.unep.org/Documents.Multilingual/Default.asp?documentid=78&articleid=1163.
[383] See: https://bch.cbd.int/protocol/parties.
[384] See: https://www.cbd.int/abs/.
[385] The UK has signed, ratified and become party to the CBD, the Cartagena protocol, and the Nagoya protocol. The US has signed but not ratified the Convention, and is not a party to it.
[386] Regulation (EU) No 511/2014 on compliance measures for users from the Nagoya Protocol on access to genetic resources and the fair and equitable sharing of benefits arising from their utilization in the EU (available at: http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A32014R0511).
[387] See section 5, paragraph 5.31ff. above.
[388] National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.
[389] Ibid.

modification technology fell to be regulated by the FDA (in the case of the GM mosquito) and the USDA (in the case of the GM diamondback moth) depending on the application.[390]

6.25 The anticipated sites of release for many genome-edited organisms are, however, not in Europe or the US but in tropical areas of sub-Saharan Africa, southern Asia and South America. Indeed, given the potential diffusion of organisms across national borders in the wild, national laws and policies are often insufficient on their own, although they can provide an important a focus for debate and engagement. There is, furthermore, a concern that conventional provisions on biosafety such as those in the *Cartagena Protocol* and regional and local instruments that transpose its basic provisions, do not take adequate account of the distinctive potential for environmental impact of gene drive systems arising from preferential inheritance. This has led to a recognised need for more specific guidance in relation, for example, to GM insects. In response to this, the World Health Organisation (WHO) has agreed guidelines on the release of GM mosquitoes (June 2014) which propose standards of efficacy and safety testing comparable to those used for trials of other new public health tools, with the aim of fostering quality and consistency among processes for testing and regulating new genetic technologies.[391] The guidelines assemble the known standards and guidance based on current research evidence and extensive professional and public consultation.[392]

Moral and societal questions identified

6.26 There are potentially significant benefits for human beings to be achieved through the use of genome editing to modify the natural environment, and scientific development in this area is, *per se*, undoubtedly consonant with identifiable moral purpose (the Baconian ideal of the 'relief of man's estate' as we noted in section 3). The moral reason to pursue and implement these developments may, however, be tempered by other considerations. These include whether there are limits to this aim itself or to how it may be pursued, whether achieving relief of one kind entails a countervailing burden that makes it morally unjustifiable (and whether this anthropocentric aim should be given paramountcy over others that may be morally valuable, such as the welfare of animals or preservation of habitats), as well as and whether relief for some entails injustice to others. Concerns about environmental risk from human interventions in open ecological systems, where the implications of biotechnology use are not only its immediate effects but also causes of a multitude of further potential adaptations in turn, invite a different kind of moral reflection to what usually surrounds relatively 'closed' interventions in biomedicine and, to an extent, in domesticated plant and livestock farming. Rather than being concentrated on the rightness of particular decisions, these concerns have spatial and temporal extension, often with uncertain limits; they invoke a different range of values and principles, such as those of sustainability, stewardship, precaution, and global and intergenerational justice.

Valorisation of the natural

6.27 Opposition to species control and (especially) engineered extinction may follow from placing significant value on outcomes other than human wellbeing.[393] One position holds that that it is simply wrong to interfere in life processes in this way, whatever the aims or the certainty of

[390] Information supplied by Sarah Hartley, University of Nottingham. See also: National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

[391] World Health Organization (2014) Guidance framework for testing of genetically modified mosquitoes, available at: http://www.who.int/tdr/publications/year/2014/guide-fmrk-gm-mosquit/en/.

[392] This was commissioned by TDR (the Special Programme for Research and Training in Tropical Diseases) and the Foundation for the National Institutes of Health. TDR is a global programme of scientific collaboration that helps facilitate, support and influence efforts to combat diseases of poverty. It is hosted at the WHO, and is sponsored by the United Nations Children's Fund (UNICEF), the United Nations Development Programme (UNDP), the World Bank and WHO. FNIH is a US charitable body established to manage funding and research in support of the mission of the NIH in the US and across the world.

[393] See section 3, above.

achieving them.[394] Another position holds that respect for the natural world and its non-human inhabitants should limit the activities of human beings. This may be of concern for the suffering of individual animals that it is thought to entail (which might suggest that it is likely to vary according to the type of animal involved).[395] Even where it does not necessarily entail animal suffering, however, this worry may still arise from concerns about the maintenance of ecological integrity and stability.[396] This raises questions about the valorisation of the 'natural' and the 'natural' relation of beings.[397] Occurrences of the normative use of 'natural' and its cognates (as opposed to its use as a descriptive adjective contrasting with 'deliberate' or 'artificial') were, however, rare in the evidence we gathered and almost always appeared in the critical literature as a 'straw man' to attack rather than as a value earnestly advanced. It may well be, therefore, that these positions are either largely absent from the discussion of genome editing (or not yet engaged with it), or have become sublimated in more sophisticated presentations.[398] In any case, it is not apparent that this is an important token in current debate, and the risk of participants 'talking past' each other in debate has not (yet) materialised.[399] The state of public discourse may be an issue that merits further attention as this debate develops in the public sphere.

6.28 Caution with regard to environmental release of genome-edited organisms is more likely to arise from concerns about different kinds of threat than from attributions of intrinsic value. Such concerns have two dimensions: moral confusion and natural catastrophe. The first concerns threats to the order and classification of beings on which knowing how to respond to them depends.[400] This appears to be less of a real concern in the case of the organisms considered for environmental release than for boundary questions about reproduction and food discussed in sections 4 and 5. The concern about ecological catastrophe resulting from interference with the 'balance of nature', however, is particularly common in relation to release of modified organisms. This holds that natural processes have operated to produce metastable ecosystems, which human intervention risks perturbing with unpredictable and potentially catastrophic results (although these results may be catastrophic only from an anthropocentric point of view).[401]

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[394] Nuffield Council (2015), *Ideas about naturalness in public and political debates about science, technology and medicine*, available at: see: http://nuffieldbioethics.org/project/naturalness/the-findings/.

[395] Research interview with Professors Glyn Hewinson and Trevor Drew (APHA).

[396] Background extinction rates not due to human action are almost imponderable, however calculations have been made that suggest that 0.1 extinctions per million species-years is "an order-of-magnitude estimate of the background rate of extinction." See: Pimm SL, Jenkins CN, Abell R, *et al*. (2014) The biodiversity of species and their rates of extinction, distribution, and protection *Science* **344**(6187), doi: 10.1126/science.1246752, at page 2). The figure the authors give for present extinction rates are approximately 1000 times higher although causes are impossible to attribute reliably. The figures might support a suggestion that even if human activity is not exceptional in kind, its effects are, directly or indirectly, exceptional in magnitude.

[397] For a discussion of the term "natural" see evidence supporting the Nuffield Council's 2015 work on *Ideas about naturalness in public and political debates about science, technology and medicine*, available at: see: http://nuffieldbioethics.org/project/naturalness/the-findings/. The paper explores five accounts of 'naturalness' deriving from: (1) scepticism about the link between nature and value, (2) belief in the 'wisdom of nature', (3) belief in natural purpose, (4) reactions of disgust and monstrosity to the 'unnatural' and artificial interventions, and (5) God and religion.

[398] See *Ideas about naturalness in public and political debates about science, technology and medicine*, op.cit.

[399] This risk was identified in *Ideas about naturalness in public and political debates about science, technology and medicine.* It may, however, be because the debate is at an early stage and has not yet fully penetrated the media, Parliamentary debate, the reports of civil society organisations, and advertising and labelling, where our earlier research found it to be used in a value-laden way. But in any case, such usages are generally performative: if participants in a public debate are 'talking past' their apparent interlocutors, it is usually because they are talking past them to their sympathisers, refusing the terms of engagement, with consequences for the quality of public debate.

[400] "Our responses to disorder and anomaly are strongly socially structured […] they are elicited by threats to our dominant systems of classification and the generally accepted ways of applying them. Structured in this way they are protective of the existing institutional order." Barnes and Dupré (2008) *Genomes and what to make of them* (Chicago: University of Chicago Press), at page 212. Christian theology has consistently offered a principle of order guaranteed by God (cf. the medieval trope of the Great chain of being (*scala naturae*).

[401] The best known expression of the idea that the earth and its component sub-systems function globally as a self-regulating system that can be perturbed in unpredictable ways by interventions that appear to be safe or low risk in the short-term is found in the Gaia hypothesis, put forward by James Lovelock in Lovelock J (1979) *Gaia: a new look at life on earth* (Oxford: Oxford University Press).

6.29 There are biosafety concerns about genome editing research and gene drive research involving genome-edited organisms, where the system is not deemed ready for environmental release.[402] (A fuller discussion of biosafety follows in section 7.) These, however, elide substantially with questions about the consequences of environmental release, which in turn bear on decisions about if and when release may be appropriate.

Precaution

6.30 As noted above, the *Cartagena Protocol* gives effect to the 'precautionary approach' set out in Principle 15 of the *Rio Declaration on Environment and Development*.[403] Whereas the latter is ostensibly about intervening to prevent uncertain environmental degradation the former explicitly orientates this towards the introduction of possible new environmental threats from biotechnologies. Precautionary approaches are proposed where substantial uncertainties cannot be excluded which, due to system effects, might include serious and undesirable consequences that may not be apparent in the short term, and which, were they to materialise, would be difficult or impossible to reverse.[404] In view of the gravity of potential consequences, precautionary thinking requires that reasonable measures should be taken to anticipate them before there is scientific proof of their likelihood.[405]

6.31 Precautionary approaches have been discussed at length in the relevant literatures and in a number of Nuffield Council publications.[406] This is not the place to engage in a sustained discussion of the coherence, persuasiveness or utility of the various formulations. Two points from previous discussions bear emphasising, nevertheless, relating to symmetry and to scope. The first is that a precautionary approach should be distinguished from simple risk assessment in that it requires account to be taken not only of the foreseeable consequences of a proposed intervention but also of the consequences of *not* making the intervention, and of the possible alternatives to the proposed intervention.[407] Rather than simply assessing 'risks', this focuses attention on the complex profiles of possible benefits as well possible harms of a range of alternative options, as well as the distribution of those consequences among different people and places.[408] The distinction between technology-focussed and challenge-focussed perspectives on precautionary thinking becomes evident in the contrast between proposals to trial GM mosquito technology in order to gather evidence on which to base a risk assessment and those to engage

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[402] On biosafety with regard to gene drives see: Akbari OS, Bellen HJ, Bier E, *et al.* (2015) Safeguarding gene drive experiments in the laboratory *Science* **349**(6251): 927-9.

[403] The related 'precautionary principle' is also a vexed feature of the regulation of environmental release of GMOs in the European Union.

[404] On the use of a precautionary approach in the expectation of hidden tail risks see response to *Call for Evidence* by Rupert Read; Taleb NN, Read R, Douady R, Norman J, and Bar-Yam Y (2014) *The precautionary principle (with application to the genetic modification of organisms)*, working paper of the New York University Extreme Risk initiative, available at: http://arxiv.org/pdf/1410.5787v1.pdf.

[405] Formulations of this principle vary considerably but most encapsulate the basic idea of acting to mitigate a credible threat to human wellbeing or the environment in the absence of evidence or consensus of the likelihood of it occurring. This is often said to shift the burden of proof onto innovators to demonstrate that their innovation is not harmful. The strict principle has been criticised as being incoherent (see, for example, Sunstein CR (2005) *Laws of fear: beyond the precautionary principle* (Cambridge: Cambridge University Press). It has also been suggested that it should be regarded more as a rhetorical and political gambit than as a decision tool.

[406] See: Nuffield Council on Bioethics (1999) *Genetically modified crops: the ethical and social issues* and *The use of GM crops in developing countries: a follow-up discussion paper* (2003), available at: http://nuffieldbioethics.org/project/gm-crops/; Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice, and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/; Nuffield Council on Bioethics (2014) *Submission to the House of Commons Science and Technology Committee inquiry: GM foods and application of the precautionary principle in Europe*, available at: http://nuffieldbioethics.org/wp-content/uploads/Submission_to_GM_inquiry_Nuffield_Council_on_Bioethics.pdf.

[407] Target Malaria advance its strategy on the strength of "the precedent that all successful malaria control programs to date have relied on attacking the mosquito vector rather than the parasite itself". This is persuasive without being convincing – we have remarked on the historic underfunding of Malaria research. [In the case of dengue, for example, the Eliminate Dengue programme, which uses a naturally occurring bacterium (Wolbachia) that reduces the ability of mosquitoes to pass dengue between people, is an alternative to Oxitec's vector control strategy. See: http://www.eliminatedengue.com/program.

[408] The *Cartagena Protocol*, for example, is risk focussed and does not explicitly take account of the benefits to human health of biotechnology use: "The Parties shall ensure that the development, handling, transport, use, transfer and release of any living modified organisms are undertaken in a manner that prevents or reduces the risks to biological diversity, taking also into account risks to human health." It is therefore silent on whether benefits to human health, for example, should be traded off against risks to the environment. See: https://bch.cbd.int/protocol/text/.

broadly before the technology is trialled.[409] The main issue with the phased approach is not the biosafety risks associated with well-designed and managed trials, but with the progressive closing down of the framing of successive questions, and the growth of technological momentum as experience of use and quantity of evidence increases.[410] Responsible innovation approaches that involve programmed break points and broader reflection at each stage have emerged to address this.[411]

6.32 The second point is that a precautionary approach must acknowledge uncertainties on all sides (those that relate to forbearance as well as different possible interventions), and take into account that different sets of consequences may be valued very differently by different people affected.[412] It should not, therefore, be restricted to a single dimension of scientifically measurable benefit or harm (e.g. harm to a defined human population in terms of projected morbidity or mortality), or to idealised experimental conditions.[413] A study by Sarah Hartley of the University of Nottingham, concerning the involvement of non-state actors in European risk assessment policy for genetically modified animals, supports the contention that "experts make decisions when policy-makers fail to acknowledge the limitations of science for risk decision-making."[414] Precautionary thinking involves the disciplined exercise of imagination, and the degree of uncertainty, which is necessarily related to the complexity of the system, demands proportionately broader engagement with the different interests that may be affected. This can only realistically be carried out in the context of a specified area of innovation, rather than abstractly in relation to a given

[409] The first is position was expressed by the House of Lords Science and Technology Select Committee in its report *Genetically modified insects* (2015), available at: http://www.publications.parliament.uk/pa/ld201516/ldselect/ldsctech/68/68.pdf (respectfully rejected in the subsequent government response) and in the response tour *Call for Evidence* by Target Malaria: "risk discussions.[…]. can only be effectively done when risk assessments can be carried out." Target Malaria envisage deployment within five to 10 years (from 2016) to allow safety and efficacy testing, and a full risk assessment. (The Chair of the Nuffield Council on Bioethics, Professor Jonathan Montgomery, gave oral evidence to the committee. Sir Roland Jackson, a member of the Council, also gave evidence in his capacity as executive Chair of Sciencewise.) It is also reflected in the concerns expressed in the NAS *Gene drives on the horizon* report that the Convention on Biological Diversity (CBD) is too precautionary and may inhibit gene drive research. It notes, with concern, that countries are now developing Cartagena-based regulatory systems "predicated on a strong precautionary, nearly preventative approach, which may restrict further gene drive research out of a precautionary concern about gene drives' intrinsic ability to spread and persist in the environment." National Academies of Sciences, Engineering, and Medicine (2016) *Gene drives on the horizon: advancing science, navigating uncertainty, and aligning research with public values* (Washington, DC: The National Academies Press), available at: http://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and, at page 8.

[410] Even accumulating *unfavourable* evidence may contribute to the momentum, since the accumulation of evidence gives the technique a 'scientific basis', and generates 'scientific problems' that invite successive stages of research to address, compared with alternative (un-trialled) technology pathways that look increasingly 'speculative' or 'traditional' by contrast.

[411] Macnaghten P, Owen R, Stilgoe J. et al (2014) Responsible innovation across borders: Tensions, paradoxes and possibilities *Journal of Responsible Innovation* **1**(2): 191-9.

[412] The response to our *Call for Evidence* by EcoNexus, for example, contrasts precaution with risk-benefit analysis and points out uncertainty of most proposed potential benefits as well as what we know about DNA with what we know about the consequences of a DNA alteration in a 'total' sense. Their point is that possible benefits are usually – erroneously – presented as less uncertain than possible harms. They express concern about a mechanistic conceptual approach with "underlying assumptions that living organisms are basically machines that can be adjusted and refined as in mechanical engineering."

[413] "Possibly the claims today represent unbounded enthusiasm over the huge potential of gene drives. Then I ask those issuing promises to bear in mind the battle against malaria will take place under uncontrolled and uncontrollable conditions with sometimes uncooperative weather, logistical complications and just plain unforeseeable issues. We live in a world in which workers vaccinating children against polio have been assassinated. It can be a tough place to conduct field trials, too." Anonymous response to *Call for Evidence*.

[414] The concern, Hartley explains, "is not that the political is shaping the scientific, but that the scientific is shaping the political and in doing so masking political choices being made by scientific experts." Hartley S (2015) Policy masquerading as science: an examination of non-state actor involvement in European risk assessment policy for genetically modified animals *Journal of European Public Policy* **23**(2): 276-95, at page 290.The earlier contention was made in Millstone E, Van Zwanenberg P, Marris C, Levidow L, and Torgersen H (2004) *Science in trade disputes related to potential risks: comparative case studies*, European Commission technical report series, available at: http://ipts.jrc.ec.europa.eu/publications/pub.cfm?prs=1203.

technology.[415] Such reflection can help to illuminate the issues most relevant to the governance of innovation, which may not be those that are most apparent to the innovators.[416]

6.33 In framing the potential benefits and costs of particular technological strategies to address societal challenges, such as the infectious disease burden, it is generally accepted that a morally appropriate approach must have reference to the knowledge, interests and values of the local communities in affected areas. Engaging with such interests is usually thought to underwrite the innovators' 'social licence to practise'. Such dialogue is more effective when framed around challenges rather than specific technologies, partly because it helps to redress asymmetries of information between 'experts' and 'non-experts' (or experts of different kinds), and partly because it avoids the hypothecation of societal challenges to particular technological solutions and of technologies to particular societal challenges, thereby avoiding 'lock-in' at the level of public discourse.[417] Such procedures are, however, vulnerable to failure through, for example, lack of empowerment of local communities and of effectiveness of NGOs and other actors.[418] This may depend on the extent to which interested citizens are able (among other things) to frame questions and risks to be addressed, to participate directly in decisions, to make effective representations in the decision making process, to hold decision makers to account democratically and to have free access to rationales for decisions.[419] Political decision making is particularly vulnerable in areas with underdeveloped democratic systems.

6.34 A second question is the extent to which these procedures may be legitimately constrained or overridden by external considerations. This is particularly difficult where, for example, local population health priorities may be overridden in the interests of protecting biological diversity – or *vice versa*. This requires a disentangling of relationships, priorities, values and responsibilities between local, national, regional and global levels. Even where such a delicate disentangling can be accomplished a further concern must arise where fragile governance systems are pushed into crisis in emergency situations, such as those created by sudden outbreaks of epidemic disease.[420] It may be difficult, in such circumstances, to forestall urgent or precipitate action by governments who, understandably, put the immediate threats to the lives and health of their citizens ahead of concerns about biodiversity and the protection of world heritage.

Complexity and reversibility

6.35 A significant difficulty in predicting the effects of environmental release of gene drive systems is the complexity of the natural ecological context in which they are released (or to which they may spread). As noted above, 'ecological risk assessment', which aims to identify causal pathways and quantify the probability of different outcomes is only one input to responsible governance of innovation. As the complexity and uncertainty of the mechanism and outcomes increases, the

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[415] As Target Malaria made clear in their evidence it is necessary to assess "each application of this new technology on a case by case basis, considering the specific characteristics of each product developed, its intended use and conditions of use" to avoid oversimplification and generalisation. Target Malaria, responding to *Call for Evidence*.

[416] See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice, and the public good, available at:* http://nuffieldbioethics.org/project/emerging-biotechnologies/. These might include, for example, the different priorities given to different risks by potentially affected communities.

[417] On framing in relation to challenges, see response to *Call for Evidence* by BBSRC and MRC: "A Sciencewise-commissioned review of public dialogue on GM crops and food concluded that dialogue is more useful when challenges rather than technologies are discussed, e.g. how can we produce food sustainably?" (the review is available at: http://www.sciencewise-erc.org.uk/cms/assets/Uploads/Talking-about-GM.pdf). On hypothecation, see *Emerging biotechnologies* (op. cit.).

[418] See: Nuffield Council on Bioethics (2012) *Emerging biotechnologies: technology, choice, and the public good, available at:* http://nuffieldbioethics.org/project/emerging-biotechnologies/.

[419] Hartley S (2015) Policy masquerading as science: an examination of non-state actor involvement in European risk assessment policy for genetically modified animals *Journal of European Public Policy* **23**(2): 276-95; see also chapter entitled: "The treatment of social and ethical concerns in regulatory responses to agricultural biotechnology: an historical analysis" submitted in evidence as part of response to *Call for Evidence* by Sarah Hartley. Hartley surveys the literature on the involvement of non-state actors in risk management and the usurpation of decision making by experts, and uses Arnstein's 1969 ladder of citizen participation.

[420] Note, for example, calls for acceleration of work on modified mosquitoes to combat the outbreak of zika virus in Brazil ahead of the 2016 Rio Olympics: https://www.hhs.gov/about/news/2016/06/27/hhs-calls-center-innovation-accelerate-zika-vaccine-development.html and http://www.independent.co.uk/news/world/americas/zika-virus-president-obama-calls-for-rapid-development-of-tests-vaccines-and-treatments-to-combat-a6837511.html.

level of confidence in any such prospective assessment will become proportionately diminished. In such circumstances, the information supporting a deployment decision at any point will quickly become outdated; adaptive innovation, close monitoring, and the availability of controls and effective remedial interventions become proportionately more important than complex prior assessment models. A precautionary approach might seem to align with the epicurean-sounding principles such as that of causing the 'least possible degree of permanent perturbation' but, as this may depend on the complexity of the system as much as the magnitude of the intervention, it is not always clear what intervention would satisfy such a principle.[421]

6.36 A proposed technical mitigation against the risk of undesirable outcomes associated with the deployment of gene drive systems is the possibility of reversing them by introducing a second ('reversal') drive. In complex systems, there must be real concerns about whether this could undo or actually compound any environmental damage.[422] (Implicitly, it would also restore the original problem that it was designed to address.) This may be mitigated if success of the first drive were suggestive of a successful second drive; furthermore, restoring a trait once perceived as harmful would be justified if it were no longer harmful (for example, for disease vectors where the disease had been eradicated) or if the benefits were now thought to be outweighed by adverse effects.

Global justice and technology transfer

6.37 A very important set of issues arises when advanced biotechnologies that are developed in high income countries with an advanced research base will be used initially (or primarily) in low or middle income countries with significant internal inequalities of income or political power among citizens. The Nagoya Protocol was intended to redress the perceived unfairness of international bioprospecting and the exploitation of sovereign natural resources. The issue of 'benefit sharing' as construed by the Protocol, however, loses purchase on much of the biotechnology involved, whose development depends increasingly on computer-aided design rather than working with genetic resources.[423]

6.38 Concerns about international research and technology transfer are complex but have been raised in the past in relation to the behaviour of the pharmaceutical industry with regard to low income countries. These range from the exploitation of economically disadvantaged people as research participants, 'shopping around' among areas subject to lower or less well enforced standards of conduct ('regulatory arbitrage'), seeking advantageous deals with local authorities with inadequate political accountability, increasing technological or economic dependency on the donor countries, paternalism with regard to access to technology or technology options, creating unnecessary and inefficient 'high tech' solutions to problems for which less lucrative 'low tech' solutions are available, or, by seeking to empower communities, disrupting internal structures of

[421] "[…] for many diseases it is feasible to break the chain of transmission without permanently fracturing the backbone of the ecosystem genetic network. For example, precisely targeted tools like ONRAB or Raboral V-RG can control rabies without any genetic legacy effects by vaccinating wild animal reservoirs. Perhaps the least risky first deployments of genetically modified wild organisms might be to emulate the Oxitec strategy to modulate mosquito vector populations (http://www.oxitec.com/). Analogous to the sterile insect methods used in the past to interrupt pest reproduction, this approach could harness the potential of genetic methods to achieve specifically aimed impacts without permanently modifying the genetic information of the targeted population." Anonymous response to *Call for Evidence*.

[422] "These attempts to downplay concerns about potentially deleterious gene drive impacts are preposterous; the proffered solutions are cascading hypotheses, not bona fide remediation strategies." Anonymous response to *Call for Evidence*. It was also suggested in this response that the *Call for Evidence* should have included issues such as: "How will risk assessments for proposed gene drive releases be conducted and the corresponding results conveyed accurately to the general public and decision makers?" and whether it is "reasonable to believe we will be able to project all impending issues or detect unanticipated consequential changes that only emerge after extended periods in time to control or reverse them?" On overwriting drives see DiCarlo JE, Chavez A, Dietz SL, Esvelt KM and Church GM (2015) Safeguarding CRISPR-Cas9 gene drives in yeast *Nature Biotechnology* **33**(12): 1250-5 and Esvelt KM, Smidler AL, Catteruccia F and Church GM (2014) Concerning RNA-guided gene drives for the alteration of wild populations *eLife*: 10.7554/eLife.03401, available at: https://elifesciences.org/content/3/e03401.

[423] See, for example, Bagley MA (2015) *Digital DNA: the Nagoya protocol, intellectual property treaties, and synthetic biology*, Wilson Center Synthetic Biology project, available at: http://www.synbioproject.org/publications/digital-dna-nagoya-protocol/.

power or authority with unintended consequences.[424] This is not to say that research consortia and firms in the biotechnology and pharmaceutical sectors, as much as any other, are not striving to promote social wellbeing while either operating on a non-profit basis or making profits at a level that may be reasonable to compensate for the costs of innovation.[425] Nevertheless, what constitutes a 'benefit' for a particular community cannot simply be assumed in the absence of effective local political processes, and the acknowledgement of potential unintended or socially undesirable consequences may argue for new and more radical thinking about innovation systems, including pricing and IP policy.[426] Many researchers and companies, indeed, see their mission as both ethical and empowering for local communities.[427] Nevertheless, the extent to which local communities are empowered or enabled to benefit from imported biotechnologies, and the requirements that are needed to ensure that they are not disadvantaged even by well-meaning technology transfer, requires careful consideration that takes into account the social conditions, power structures and preferences of the communities concerned.

Other uses of CRISPR-enabled gene drives

6.39 Not all genome editing interventions may be to address an imminent public health or environmental threat. It is conceivable that genome editing may be contemplated to improve or enhance already safe environments, allowing the expression of human preferences over the composition of the biosphere, rather than addressing urgent needs. This raises the question of when, and under what conditions, particularly if there is an irreducible risk of harm, it might be appropriate to use biotechnologies to give expression to collective human preferences over and above meeting some commonly recognised need.

6.40 A further, and substantial set of concerns relates to the use of genome editing, particularly with gene drives, for malicious purposes, for example to trigger an ecological catastrophe. Such a use would at present require significant technical resources: although the use of CRISPR by amateurs has been reported, the creation of gene drives in such a context currently still seems beyond the ability of most amateurs.[428] Dual use potential of genome editing will be considered further in section 7.

Conclusion

6.41 The convergence of gene drive and genome editing technologies raises a range of concerns about biosafety and environmental release that are similar to those that have been raised about potentially hazardous biological research and genetically modified organisms. A major potential

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[424] On research in developing countries, see Nuffield Council on Bioethics (1999) *Genetically modified crops: the ethical and social issues* and *The use of GM crops in developing countries: a follow-up discussion paper* (2003), available at: http://nuffieldbioethics.org/project/gm-crops/. On high tech solutionism: see anonymous response to *Call for Evidence*: "Some proposed uses of gene drives appear to be high-tech solutions in search of problems." (The response cites dengue and lyme disease as having viable alternative solutions.)

[425] "while research capability might be predominantly in the hands of developed country laboratories, it can be argued that the most important and valuable benefits would be experienced by developing countries, with relatively little local investment. This situation changes the benefit sharing conversation, since typically the concern has been the exploitation of developing country resources for the benefit of developed countries. In a sense, the applications of gene drive approaches for malaria control could reverse the traditional benefit sharing equation." Response by Target Malaria to *Call for Evidence*.

[426] See Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good*, available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/, chapter 9; Pogge T, Rimmer M, and Rubinstein K (Editors) (2010) *Incentives for global public health: patent law and access to essential medicines* (Cambridge: Cambridge University Press).

[427] Target Malaria states that all its researchers have made "a 'global access' promise that specifies that the technology will be made available and accessible to developing world countries at an affordable price. In addition, the technology profile would provide equal access regardless of economic status, and would not require behavioural changes." Response to *Call for Evidence* by Target Malaria.

[428] Ledford H (2015) Biohackers gear up for genome editing *Nature* **524**(7566): 398-9. According to the Royal Society, "gene editing techniques are already widely used and similar to other areas of research there is the possibility of dual use of concern. Due to the speed of the development in the sciences, the decreasing costs and the increasing ease of use, the technological barriers to acquiring a biological weapon have been eroded. The skills and resources required remain considerable implying that it would likely require the backing of a nation state, however these barriers are likely to be rapidly eroded over the next few years with new technologies. […] the increased precision of gene editing technique also means that changes introduced may be effectively 'invisible', making forensic investigation and attribution difficult" (response to *Call for Evidence* by the Royal Society).

for benefit, as well as a major source of concern, is the use of genome editing systems with gene drives that are designed to spread a deliberate modification rapidly throughout a population in the interests of public health. Given the potential for suppression or amplification of effects owing to properties of ecological systems that are difficult to predict or to control, the environmental release of genome edited organisms when combined with gene drives needs to be approached with caution.

6.42 Precautionary approaches, while offering clear indications of principle are extremely difficult to give effect to through regulatory practice. The approach embodied in the *Cartagena Protocol*, which is being elaborated in local measures around the world, is not well suited to genome editing enabled by gene drive systems, which, if they work, may work in an escalating pattern until a population becomes saturated. Ecological risk assessment approaches may not be sufficiently well developed to inform decisions about gene drives; strategies to contain or mitigate are desirable, but those that rely on technical means to reverse the effects of the gene drive may not adequately address systemic effects and irreversibilities that follow from the initial deployment of the drive. The introduction of gene drives therefore requires flexible and adaptive models of innovation governance ('responsible innovation') that involve built-in opportunities for reflection and break points, and especially that avoid creating technological momentum around contingently preferred alternatives. Finally, particular attention needs to be given to issues of global justice in technology transfer from high-income countries to low- and middle-income countries.

6.43 The benefits of the responsible environmental release of genome-edited organisms could be significant and transformative, but the potential hazards are substantial and it is unlikely that the risk of unintended and undesirable consequences will be eliminated completely. This makes the political legitimacy of any decision especially important. Based on the experience with genetically modified mosquitoes to date, and the procedures required to bring conventional GMOs to market, and in the context of an existing and evolving international policy framework, it is likely to take a number of years before genome edited organisms are ready for large scale release into the wild. Well before then, the substantial ethical and societal questions identified above – including how the natural world and different states that human intervention may bring about are valued, of how to ensure that an intervention is just, of where the locus of different decisions should lie – will need to be addressed.