Section 5

Food

Section 5 – Food

Outline

From the dawn of recorded history, and probably earlier, to the present day humans have sought to improve the quality and availability of food through selective breeding. New breeding techniques, including those involving genome editing, are described in the context of induced mutagenesis and other genetic engineering. The similarities and differences between genome editing and other alteration techniques are discussed. It is noted that the significance given to these similarities and differences may have significant implications for both the technology and food production. Different approaches to the regulation of foods and genetically modified organisms in the EU and North America are described and current areas of uncertainty noted. The potential impacts of uncertainty on science and industry are identified as matters of concern.

Reasons why genome editing may have less transformative potential in plant breeding than in animals are elaborated. Nevertheless, genome editing is a useful research tool for a variety of aims and has the potential to accelerate genetic gain in breeding programmes. The strong shaping of research by economic conditions that apply to commercial plant breeding are considered.

In animals, genome editing has made possible research that was not previously feasible. Limitations to achieving desired modifications are compounded by the low efficiency of the procedures used to produce genetically modified livestock, although genome editing has potential advantages over other approaches in terms of safety and controllability. Animal-based food products are subject to similar regulatory requirements as crop plants as well as additional requirements relating to animal welfare, which are outlined. The impact of genome editing on areas of livestock research relating to yield, animal health and environmental adaptation is described.

Many of the moral and societal issues are common to plants and animals, but they are not simply about securing adequate levels of consumption of safe, nutritious food. Lack of evidence of harm to human health of GMOs is cited as a reason to move to product regulation, based on substantial equivalence to existing products. This has not, however, removed concerns about uncertainties that science is unable to eliminate, the significance of which remains contested. Critical examination of the significance of uncertainty suggests it is grounded in a variety of different values, including attitudes towards genome technologies and consumer choice. The use and limitations of the precautionary principle and precautionary approaches are discussed. A critique of the framing of societal challenges is found to be indispensable in the formulation of ethical public policy responses. Different visions of future food production are considered in relation to their framing assumptions, revealing that what is needed for ethical public policy is an agreed presentation of the common challenge and the conditions for constructive engagement between different actors and interests.

Conclusions are drawn from the discussion about the significance of the emergence of genome editing as a driver for the critical reappraisal of moral and regulatory frameworks governing food production, the need to take a challenge-led approach to this reflection, and the need to consider the proper scope and jurisdiction of policy and regulatory measures

Introduction

5.1 Settled human societies have long sought to improve their food supply, in terms of quality (nutrition, preservation, appearance, taste etc.) and the ease of obtaining it (enclosed livestock, improved crops, etc.). This has exerted a tremendous evolutionary constraint that has left almost nothing that is commonly eaten today (except perhaps fish) biologically unaltered by human intervention and has rendered many wild antecedents extinct.[224] This section examines the potential impact of genome editing on plants and animals produced for food, principally for human consumption.[225] Uses of genome editing in wild animals and plants will be discussed in section 6. Genome editing of domestic plants and animals other than for food and related purposes, such as for show, competition or companionship will be noted where relevant.

[224] There is an irony, therefore in the fact that the first genetically modified animal approved for human consumption (by the US Food and Drug Administration) is the AquAdvantage salmon; see: http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm466214.htm.

[225] For the purposes of this part we discuss fungi along with plants since the issues are similar (noting that an FDA decision that a genome edited mushroom should not be regulated as a GMO has significant implications across both kingdoms – see: Waltz E (2016) Gene-edited CRISPR mushroom escapes US regulation *Nature* **532**(7599): 293.

Plants

5.2 The domestication of food crops began in the Neolithic period, over ten thousand years ago, a process that has continued to the present day. Domestication depends on mutagenesis: random or induced genomic mutations are fixed, giving rise to desirable traits, such as high yield, reducing genetic diversity in domestic populations and leading to a more homogeneous set of characteristics (phenotype).

Genome editing in the context of a range of plant breeding techniques

5.3 Many molecular techniques have recently been developed for use in plant (crop) breeding. These sit beside traditional breeding techniques that involve the selection of mutations that either occur naturally or are produced through the use of chemical mutagens or radiation. Selective breeding selects for overt (phenotypic) characteristics of an organism that are exhibited in a particular environment. In this case the genetic (or epigenetic) contribution to the phenotype, which may be related to a single gene variant or, perhaps, to hundreds of genes, may be unknown. Genetic engineering (including genome editing) generally involves the modification of specific genes to identify their effect on the phenotype and to reproduce this effect in populations. Whereas selective breeding can only work with variations that are present in the precursor organisms (as a result of natural or induced random mutagenesis) genetic engineering allows the introduction of characterised genes from other organisms, including from other species, to give rise to a phenotype that may be radically novel in the engineered strain.[226]

5.4 First generation plant genetic engineering most often involved the transfer of cloned genes from one organism to another (often using a bacterial vector, which inserts the gene at a random site in the organism) to produce a so-called 'transgenic' organism. Developments in understanding of the genome have given rise to a suite of New Breeding Techniques (NBTs), as they are collectively known. These have been enabled by advances in genome sequencing (including the increase in speed and reduced cost with next generation sequencing) and DNA assembly, both key underpinning technologies across molecular biology, as well as developments in data technologies and bioinformatics.

5.5 NBTs make directed changes to the genome without the need to introduce genes or regulatory sequences from another species.[227] The European Commission's New Techniques Working Group, established to review the applicability of Community GMO legislation, currently has under review the following NBTs:[228]

- Oligonucleotide Directed Mutagenesis (ODM)
- Zinc Finger Nuclease Technology (ZFN) comprising ZFN-1, ZFN-2 and ZFN-3
- Cisgenesis and Intragenesis
- Grafting
- Agro-infiltration
- RNA-dependent DNA methylation (RdDM)
- Reverse breeding
- Synthetic genomics

5.6 Whereas most of the products of first generation genetic engineering, known as genetically modified organisms (GMOs), involved the insertion of DNA, genome edited plants may be altered

[226] See also response to *Call for Evidence* by the Royal Society.
[227] An exception is the use of genome editing to insert transgenes using sequence-specific nuclease technology (SSN-3). See: Schaart JG, van de Wiel CCM, Lotz LAP, and Smulders MJM (2016) Opportunities for products of new plant breeding techniques *Trends in Plant Science* **21**(5): 438-49
[228] See: http://ec.europa.eu/food/plant/gmo/legislation/plant_breeding/index_en.htm. For a comparative survey of some NBTs, see: Schaart JG, van de Wiel CCM, Lotz LAP, and Smulders MJM (2016) Opportunities for products of new plant breeding techniques *Trends in Plant Science* **21**(5): 438-49.

in a way that is identical to natural or induced mutation, albeit that the mutation is specific and targeted. The ability to produce a specific and targeted mutation avoids the need to screen hundreds of thousands of crosses, (for example, between a crop and mutagenized plants or a wild relative containing the desired sequence) to identify those with the desired traits. The selective changes enabled by genome editing therefore significantly reduce the time and numbers of plants involved in achieving a desired mutation that might otherwise be sought by using methods of random mutation and selection.[229] Since genome editing techniques may also be used to introduce longer DNA sequences, including from other species, it is important to consider the nature of the product rather than the technology alone to determine safety and the regulatory process needed.[230] Similarities and differences between existing and prospective techniques of plant breeding are matters of current dispute, on which hang both moral and regulatory responses. The outcomes of these disputes may have far-reaching implications for how the technologies develop and, ultimately, how systems of food production evolve to meet global food security challenges.

Regulation of genetically altered food

5.7 The regulation of genetically altered food differs among jurisdictions in a number of respects, including the scope of regulation and how this is defined, the focus of regulation and the requirements placed on those subject to regulation. In the EU, a key distinction is made between genetically modified organisms (GMOs) and food that does not fall into this classification, albeit food that may have been subject to other alterations. All food and feed, including non-GMO food and feed, are subject to the 'General Food Law Regulation', which provides for the safety of food and animal feed, and to regulation by the European Food Safety Agency.[231] Additionally, a number of instruments apply specifically to GMOs in relation to containment and environmental risk (the release of GMOs into the environment, the movement of GMOs across borders, and the factors that can be taken into account), safety of GMOs for consumption by people and livestock, and traceability.[232]

5.8 From a food safety perspective, the key principles of all regulatory systems require demonstration that manipulation of the crop has not added a toxic or allergenic component and that, with the exception of the introduced genes, the composition of the GM plant is indistinguishable from the unmodified crop. In addition, from an ecological perspective, it is necessary to demonstrate that the GM crop will not become a weed, or threaten endangered or beneficial species. These principles clearly have value in relation to all new crop varieties, by whatever the means they are produced, although it is reasonable to debate the level of precaution and the extent of data required in different cases.

5.9 Other jurisdictions also have distinct provisions for the regulation of GMOs, although they may be engaged by different classification criteria. In the EU, the classification of GMOs is based on

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[229] Response to *Call for Evidence* by the British Society of Plant Breeders.

[230] "Some genome edited plants, those that contain no transgenes and only a minute change in the sequence of the DNA in a specific gene or genes, are different from GM plants. They are more similar to plants produced by mutagenesis technologies, which are not regulated as GM. Plants in which genome-editing technologies have been used to insert new DNA at a specific genetic location are similar to plants currently regulated as GM." Response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

[231] Regulation (EC) No 178/2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2002:031:0001:0024:en:PDF.

[232] See, respectively: Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms, (available at: http://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF0, amended by Directive (EU) 2015/412 as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory (available at: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L0412&from=EN) and Regulation (EC) No 1946/2003 on transboundary movements of genetically modified organisms (available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:287:0001:0010:EN:PDF); Regulation (EC) 1829/2003 on genetically modified food and feed (http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003R1829&from=en0); and Regulation (EC) 1830/2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms, available at: http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:268:0024:0028:EN:PDF.

whether the alteration has been made "in a way that does not occur naturally by mating and/or natural recombination", and is elaborated as 'at least' requiring the use of a listed technique.[233] This is conventionally thought to capture transgenic organisms but not those with alterations that might be achieved through natural breeding (however demanding), including those produced by cisgenics (where new genes are introduced from closely related organisms) and, arguably, certain genome editing protocols. In Canada, by contrast, all foods that are genetically altered, including by conventional breeding, are classed as 'novel foods' without further distinction. All novel foods require a pre-market notification to Health Canada (the Canadian federal department of health), following which a full safety assessment is made. This is done on the basis of the characteristics of the product itself, rather than the process by which it was produced.[234] In the US, genetically altered foods are regulated by the FDA. Where they are like substances currently found in food ('generally recognized as safe' – GRAS) they do not require separate pre-market approval. However, where a GMO product "differs significantly in structure, function, or composition from substances found currently in food," pre-market approval of the substance as a 'food additive' would be required.[235]

5.10 The subtlety and control possible with genome editing tools like CRISPR-Cas9, has led to strong proposals that products should not be subject to the extensive regulatory studies currently required for genetically-modified plants in Europe.[236] In many cases achieving the same DNA sequence and phenotype would be equally feasible through selective breeding. Genome editing also presents problems for analysis-based traceability, since the technique leaves no tell-tale genetic evidence in the final product.[237] However, it would be a commercial requirement for a new plant variety that it be registered for Plant Variety Protection, which guarantees intellectual property rights to breeders of new plant varieties.[238] This provides an additional reason to secure traceability, although this may depend on documented chains of custody rather than distinctive features of the product.[239]

5.11 The regulatory response to genome-edited foods in general remains uncertain. A number of crops produced using relevantly similar techniques have been approved for market in some countries.[240] Rulings have been handed down by the Animal and Plant Health Inspection Service (APHIS), an office of the US Department of Agriculture, that place genome-edited products in development

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[233] Directive 2001/18/EC, Art.2(2). The techniques are those listed in Annex I A, part 1; additionally, techniques listed in Annex I A, part 2 are deemed not to give rise to GMOs. Genome editing does not appear explicitly in either Annex.

[234] See: http://www.hc-sc.gc.ca/sr-sr/pubs/biotech/reg_gen_mod-eng.php.

[235] FDA (1992) *Statement of policy – foods derived from new plant varieties* (1992),available at: http://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/Biotechnology/ucm096095.htm. See, generally, https://www.loc.gov/law/help/restrictions-on-gmos/usa.php#_ftn47.

[236] Jones HD (2015) Regulatory uncertainty over genome editing *Nature Plants* **1**: 14011; Strauss SH and Sax JK (2016) Ending event-based regulation of GMO crops *Nature Biotechnology* **34**(5): 474-7.

[237] […] the genes that code for the nucleases may be present at certain stages, but this is mostly temporarily, and they will not be present in the final product. Also, already technology is evolving to avoid the introduction of genes coding for the nucleases. The use of (pre- assembled) protein complexes may suffice in many instances in the future." Response to *Call for Evidence* by the Vlaams Instituut voor Biotechnologie). In cases where the induced change is identical to those found in either natural or chemically-mutagenised populations, "it will be extremely difficult if not impossible to apply simple tests for contamination such as those currently used for screening product batches for contamination by transgenic seed. The burden of proof will therefore depend on the integrity of the ownership chain." Response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

[238] Plant Variety Protection (PVP) protects the intellectual property rights of plant breeders by granting enforceable exclusivity for the marketing, sale and development of their registered varieties for a period of time (usually 20 or 25 years, or more for certain species such as trees). PVP is guaranteed by the International Convention for the Protection of New Varieties of Plants (UPOV Convention 1961, last revised 1991), which has 74 States Parties including most of the Americas and the global North, and by domestic legislation such as the US Plant Variety Protection Act of 1970 (PVPA), 7 U.S.C. §§ 2321-258. PVP overlaps but does not supplant other forms of intellectual property protection, such as patent protection.

[239] In a research interview, Professor Nicola Spence agreed that having no audit trail would make a product difficult to regulate, but she pointed out that there might be proxies for traceability: for example, isotope and mineral profiles can help to identify variety and potentially even what field it was grown in, demonstrating product integrity.

[240] For example, Cibus received market approval in the US and Canada for herbicide tolerant canola, obtained through the use of oligonucleotide-directed mutagenesis (ODM) and expect approval in other countries in 2018 (see: http://www.cibus.com/products.php).

beyond the special regulatory provisions that usually apply to GMOs.[241] The position of genome-edited products in the EU remains unclear at the time of writing and the European Commission has asked Member States not to take national decisions on the status of genome-edited products pending the release of an interpretative document.[242] This has led to concerns that persistent uncertainty is likely to lead to disinvestment, attrition of the research base (Europe accounted for 46% of research on plant NBTs in 2012) and failing international competitiveness.[243]

Applications of genome editing in food plants

5.12 The impact of genome editing techniques is, however, perhaps less revolutionary in plants than in relation to humans (see section 4) in the context of such a long history of changing the genetic characteristics of virtually all crop and ornamental plants. Plant breeding has been able to combine DNA sequences that occur naturally in a single plant, because discarding many thousands of crosses that do not have this combination is not considered to be an ethical issue, nor is the elimination of lines which contain an inherited 'abnormality'. In addition, mutation, either natural or induced, has been used to generate variations in DNA sequences, with those that produce useful phenotypic characteristics being retained. (In the gardening world, plants which contain natural mutations with a visible phenotype are called 'sports' and are highly sought after.) In some cases, it has been possible to cross different but related species to introduce traits, such as disease resistance, that do not occur within the species being improved. In plants, therefore, it has been possible to achieve many of the sorts of subtle changes in DNA sequence that are opened up in other organisms by genome editing techniques by cross breeding, or selecting natural or induced mutations that give rise to plants with the desired characteristics. The production of commercial GM crops, on the other hand, largely depends on the introduction of whole genes that do not occur naturally in plants (for example, the introduction of Bacillus thuringiensis genes from soil bacteria to give insect resistance and extensive changes to the EPSPS gene so that it codes for resistance to the herbicide glyphosate, which cannot be introduced by random mutation in natural populations).

5.13 In the laboratory, genome editing is proving to be a valuable research tool in plant breeding, including in gene discovery, producing knock-outs to study functional advantage and identification of 'safe harbours' (places where transgenes can be inserted safely without disrupting essential endogenous genes). It also supports current research into the integration of transgenes at specific positions, since the position of a gene in the genome affects its expression. Research uses have been proposed for genome editing that include traditional commercial targets such as improvements in yield and pesticide resistance. Other possible applications include inherent pest resistance (wheat resistant to powdery mildew,[244] bacterial blight-resistant rice,[245] and other causes of crop loss) that could reduce pesticide use, drought tolerance (e.g. for use in arid

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[241] Correspondence between the inventor (https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_inquiry.pdf) and the US Department of Agriculture Animal and Plant Health Inspection Service (https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf) regarding whether the 'non-browning' white button mushroom (*Agaricus bisporus*), edited to knock out some sequence using CC9, is genetically modified – although this is in relation to environmental impact rather than to consumption as food. A similar letter of comfort was received in response to a regulated article letter of inquiry from DuPont Pioneer regarding waxy corn variety produced using CRISPR-Cas9, which it intends to bring to market within a few years. (DuPont letter here: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-352-01_air_inquiry_cbidel.pdf; APHIS response here: https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-352-01_air_response_signed.pdf). See also: http://uk.businessinsider.com/dupont-crispr-corn-in-stores-in-5-years). DuPont have made and agreement with Cariobou Biosciences – a spin-out from Jennifer Doudna's lab and one of the main IP claimants on the platform technology.

[242] See: European Parliamentary Research Service (2016), *New plant-breeding techniques. Applicability of GM rules*, available at: http://www.europarl.europa.eu/RegData/etudes/BRIE/2016/582018/EPRS_BRI(2016)582018_EN.pdf.

[243] "The knowledge generated through the research on NBTs, and the product innovations that are derived from their use, are already applied for commercial products in countries outside Europe. Prolonged absence of regulatory clarity for products derived from NBTs in the EU will hamper plant-related innovation in the EU and will mean a competitive disadvantage for EU-based plant breeders." Response to *Call for Evidence* by NBT Platform.

[244] Wang Y, Cheng X, Shan Q, *et al.* (2014) Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew *Nature Biotechnology* **32**(9): 947-51.

[245] Zhou J, Peng Z, Long J, *et al.* (2015) Gene targeting by the TAL effector PthXo2 reveals cryptic resistance gene for bacterial blight of rice *The Plant Journal* **82**(4): 632-43.

conditions, as a response to climate change and food shortages in developing countries),[246] and possible increases in nutritional benefit (e.g. nutritionally enhanced staple foods),[247] health benefit (e.g. decreased presence of allergens or anti-nutritional compounds)[248] and appearance (e.g. non-browning apples, which could reduce food waste).[249] Genome editing may also contribute to the development of plant-based industrial bioproducts, which could decrease dependence on oil-based products (see section 7 below).[250]

5.14 Where CRISPR-Cas9 shows most promise is in changing alleles in a targeted way – perhaps multiple alleles at a time – in basic breeding lines. Depending on the species, conventional plant breeding may require between seven and twenty-five years to generate desired characteristics and to introduce these into stable and uniform new plant varieties.[251] Genome editing offers the potential to reduce the shortest times for 'boutique' plants by two to three years and the longer timescales by more.[252] Knowledge of plant sequences linked to performance is now developing so quickly that it is possible to define an ideotype comprising so many desirable alleles that, statistically, it would be impossible to reach in a practicable number of generations of crossing. CRISPR-Cas9 could change the alleles in a targeted way in basic breeding lines, and thereby greatly accelerate genetic gain in the breeding programme by avoiding the need to go through economically unfeasible numbers of generations to achieve the desired combination of alleles by crossing.

5.15 There is also speculation that gene drives, which cause traits to be inherited preferentially, could be combined with editing systems and applied to plants. However, since crop plant breeding is controlled in any case, to secure the inheritance of desired traits, gene drives would be of use only in wild populations. A potential application, then, might be to control plant pathogens, or to control pests and weeds by conferring or reversing pesticide or herbicide resistance (see section 6, below).[253]

5.16 Genome editing faces many of the bottlenecks traditional to plant biotechnology: the time and effort required for delivery of DNA to plant cells (i.e. getting necessary reagents across the cell wall) and the regeneration of plants containing the programmed changes. Production of plants is labour-intensive, slow and requires significant investment in technical expertise and training, which is why private sector companies such as Dow AgroSciences, DuPont Pioneer and Cellectis have been major contributors to research and development.[254] Commercial firms are also free of certain demands that apply to academic research, such as the pressure for publication and to

[246] DuPont Pioneer is developing drought-resistant corn and more vigorous, hybridising wheat using CRISPR on a time line of 5-10 years; see reports at https://www.technologyreview.com/s/542311/dupont-predicts-crispr-plants-on-dinner-plates-in-five-years/.

[247] Haun W, Coffman A, Clasen BM, *et al.* (2014) Improved soybean oil quality by targeted mutagenesis of the fatty acid desaturase 2 gene family *Plant Biotechnology Journal* **12**(7): 934-40; Clasen BM, Stoddard TJ, Luo S, *et al.* (2016) Improving cold storage and processing traits in potato through targeted gene knockout *Plant Biotechnology Journal* **14**(1): 169-76.

[248] Schaart JG, van de Wiel CCM, Lotz LAP and Smulders MJM (2016) Opportunities for products of new plant breeding techniques *Trends in Plant Science* **21**(5): 438-49.

[249] Nishitani C, Hirai N, Komori S et al. (2016) Efficient genome editing in apple using a CRISPR/Cas9 system *Scientific Reports* **6**: 31481.

[250] Response to *Call for Evidence* by the Agricultural Biotechnology Council.

[251] Response to *Call for Evidence* by NBT Platform.

[252] See responses to *Call for Evidence* by the British Society of Plant Breeders and GARNet. The likely time savings as a result of genome editing will depend on a number of factors but developments will still be subject to timescales of contingent processes, such as regulation and propagation of seed at sufficient scale for the commercial market, which take the bulk of the time.

[253] "In plants, gene drive could contribute potentially to sustainable agriculture by reversing pesticide and herbicide resistance [in weeds and pests]. More widely, it holds promise for the control of insect pests and vectors of disease." Response to *Call for Evidence* by BBSRC and MRC. The US source cited (The Wyss Institute for Biologically Inspired Engineering) notes that "By 2012, glyphosate-resistant weeds had infested 25 million hectares of US cropland." (see: http://wyss.harvard.edu/staticfiles/newsroom/pressreleases/Gene%20drives%20FAQ%20FINAL.pdf).

[254] Evidence from fact-finding meeting on plant science and response to *Call for Evidence* by the Sainsbury Laboratory and the John Innes Centre.

demonstrate some types of impact.[255] However, the necessary protection of intellectual property through the lengthy research and development (R&D) process required to bring new products to market means that there is some uncertainty about how genome editing has been taken up. Agricultural biotechnology giants appear to be awaiting developments in genome editing by the academic research base and translational research by smaller biotech firms.

5.17 A question of significant interest is whether genome editing will help to deliver 'second and third generation' crops with improved characteristics such as enhanced growth, nitrogen fixing, stress tolerance and nutritional enhancements. Given the organisation of the innovation system and the concentration of resources in the hands of commercial firms, the products that are developed are likely to be those that have greatest commercial value, which to date have been principally herbicide tolerance and insect resistance, either because other beneficial changes have been of limited effectiveness, such as stress tolerance, or of limited commercial value, such as nutritional enhancement. Much may depend on decisions about regulation: the potential of genome editing techniques (in terms of decreased cost and technical difficulty, and increased speed) may revive the opportunities for small and medium-sized biotech companies in the agricultural area and unlock development of a wider variety of traits.[256] However, these may be easily depressed by regulatory burdens, such as those that apply in Europe in the case of GMOs in contrast to conventionally-bred lines.

Livestock

5.18 Unlike in plants, genome editing in animals has not merely accelerated research but made possible research that had been previously unfeasible.[257] Because the generation time in most commercial animals is long (typically many months) and their reproductive rates are often low (for example, one offspring per generation in cattle, although as many as 15 in pigs), the backcrossing strategies that allow native genes to be used so effectively in plant breeding are considerably less productive in the case of most livestock. On the other hand, the method of reproduction, which allows the possibility of embryological micromanipulation, makes animals more amenable to certain forms of editing.[258] There are said to be three principal challenges in genome editing with regard to livestock: the technology itself (and whether it can be scaled up to commercially worthwhile levels), securing regulatory approval, and farmer and public acceptance.[259] (The first two are discussed immediately below, the third under the heading 'Moral and societal questions identified', following an overview of the range of possible applications.)

Technical challenges

5.19 The majority of genetically engineered livestock are pigs produced by somatic cell nuclear transfer (SCNT), which yields piglets of predictable genotype.[260] Although SCNT has been the method of choice to produce cloned lines of gene targeted animals there are, nevertheless, limitations in terms of the relatively low viability of cloned embryos and the difficulty of achieving genetic manipulation of isolated nuclear donor cells.[261] Recently, the CRISPR-Cas9 system has become widely used, alongside ZFNs currently in use in pigs and other large animals, and TALENs in

[255] See also: Nuffield Council on Bioethics (2014) *The culture of scientific research*, available at: http://nuffieldbioethics.org/project/research-culture/.
[256] Evidence from fact-finding meeting on plant science.
[257] Tan W, Carlson DF, Walton MW, Fahrenkrug SC and Hackett PB (2012) Precision editing of large animal genomes *Advances in Genetics* **80**: 37-97; Rocha-Martins M, Cavalheiro GR, Matos-Rodrigues GE and Martins RAP (2015) From gene targeting to genome editing: transgenic animals applications and beyond *Anais da Academia Brasileira de Ciências* **87**: 1323-48; Wang Z (2015) Genome engineering in cattle: recent technological advancements *Chromosome Research* **23**(1): 17-29.
[258] Whitelaw CBA, Sheets TP, Lillico SG and Telugu BP (2015) Engineering large animal models of human disease *The Journal of Pathology* **238**(2): 247-56.
[259] Research interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus.
[260] Whitelaw CBA, Sheets TP, Lillico SG and Telugu BP (2015) Engineering large animal models of human disease *The Journal of Pathology* **238**(2): 247-56.
[261] Ibid.

pigs, sheep and cattle.[262] As in other research, key challenges for large animal genome modification at present are to demonstrate that only defined changes are made at specific loci (avoidance of off-target effects) and to increase the efficiency with which changes can be introduced. Related to the issue of specificity, gene delivery to animals may be subject to 'insertional mutagenesis' in transgenic animals, which leads to unprogrammed gene suppression or expression.[263] Genome editing presents fewer sources of risk than conventional genetic engineering since it leaves no trace of the nuclease after it has performed its function and need not involve the introduction of extraneous (bacterial and viral) DNA as part of the delivery mechanism.[264]

Regulation of genetically altered animals

5.20 Insofar as animals and animal products might enter the human food chain (either directly or, for example, in the form of animal feed) they are subject, in most cases, to the same regulatory provisions as apply to plants. Thus, in the EU, they are similarly subject to the General Food Law and other Regulations and the Directive applying to GMOs (as applicable).[265] In the US, since the development in the 1980s of the 'coordinating framework', biotechnology products have been regulated based on their characteristics and intended uses rather than their method of production.[266]

5.21 However, to date, the only example of a GM animal being approved for direct human consumption is the AquAdvantage salmon, which was approved by the US FDA in late 2015, almost 20 years after the initial application, following an extensive review that looked at safety for humans, the impact of the change on the fish itself, and the environmental impact.[267] It is notable that, in the US, which, unlike the EU, does not require labelling of GM food, the FDA have stipulated that the AquAdvantage salmon should be labelled as genetically engineered, in recognition of the societal issues as well as scientific safety.

5.22 In addition to the health and safety provisions that apply to people working with animals in research and farming, and requirements about biosafety and environmental release that are similar to those applying to plants, research involving animals has additional levels of regulation relating to the welfare of the animals involved. In the UK this is overseen by the Animals in Science Committee (an NDPB that replaced the Home Office Animal Procedures Committee as principal source of advice to the Secretary of State, with whom the formal decision making power rests) under the Animals (Scientific Procedures) Act 1986.[268] Livestock breeding for food production is further regulated by a host of measures that include legislation and codes of practice designed to protect animal welfare on farms, in transport, at markets and at slaughter.[269]

Applications of genome editing in livestock

5.23 A number of applications of genome editing in animals have been reported or proposed. Traits currently under investigation mostly relate to improvements in yield, disease resistance, and adaptation to farming or environmental conditions. These traits have been pursued through other

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[262] Ibid.
[263] Tan W, Carlson DF, Walton MW, Fahrenkrug SC and Hackett PB (2012) Precision editing of large animal genomes *Advances in Genetics* **80**: 37-97.
[264] Ibid.
[265] Directive 2001/18/EC (environmental release), Regulation (EC) No 178/2002 (general food law regulation), Regulation (EC) 1829/2003 (genetically modified food and feed) and Regulation (EC) 1830/2003 (traceability and labelling).
[266] Carroll D and Charo R (2015) The societal opportunities and challenges of genome editing *Genome Biology* **16**: 242.
[267] The genetic alterations involve growth promoters that cause the all-female salmon grow to market size faster than farmed Atlantic salmon; see: http://www.fda.gov/AnimalVeterinary/DevelopmentApprovalProcess/GeneticEngineering/GeneticallyEngineeredAnimals/ucm466214.htm.
[268] See: http://www.legislation.gov.uk/ukpga/1986/14/contents.
[269] See: https://www.gov.uk/guidance/animal-welfare.

approaches although here, as elsewhere, CRISPR-Cas9 genome editing may have advantages in terms of its relatively low cost, technical facility, speed and efficiency.

5.24 There are two basic approaches to augmenting yield: increased fecundity and more efficient conversion of inputs into outputs. Research and breeding programmes have focussed on a number of organisms where gains in reproductive efficiency can be made, for example, chickens that produce only female offspring for egg-laying, and cattle that produce only male offspring, which are more efficient than females at converting feed to muscle. [270] Applications to generate animals that are more productive with regard to inputs include, for example, pigs that can be fattened with less food, Brazilian beef cattle that grow large muscles, yielding more meat, and cashmere goats with greater muscle mass that also grow longer hair used in the production of soft sweaters.[271]

5.25 A number of genome editing applications relate to the health and welfare of animals. Many of these concern adaptation to environmental conditions, particularly those of intensive livestock farming, such as space and diet, and where close proximity to other livestock might facilitate the spread of infectious disease. These include hornless ('polled') cattle that can be kept in close proximity in confined spaces with lower risk of injury, and miniature pigs, which were originally purposed for their ease of husbandry in scientific research but which have since found a market as novelty pets.[272] Disease resistance is a particular area of active research given its commercial significance. One major advantage of engineered disease resistance in livestock is that it could, in principle, reduce the use of prophylactic antimicrobials in farming, as these have been cited as a significant cause of emerging antimicrobial resistance more generally.[273] Once again, commercial breeds are the main targets.

5.26 Resistance to viral pathogens is an area of major interest in poultry and pigs. For example, researchers at Roslin Institute in Edinburgh have produced a genome-edited Large White breed of pigs (in which the editing machinery was injected into the cytoplasm of the zygote), modified to be resistant to African swine fever virus.[274] This disease has a high (90%) mortality rate and represents a significant threat to the pig farming industry, currently menacing the borders of Europe. The pigs were edited to delete a few base pairs; this change results in an immune reaction emulating that of wild warthogs, which have a more effective immune response to the virus.[275] In the longer term it might be possible to contain swine and bird flu by genome editing their hosts, reducing their ability to act as reservoirs for zoonotic diseases that might affect humans and hence the frequent need for new human flu vaccines. To date, the technical strategies have achieved less success in chickens than in pigs.[276] Resistance to bovine tuberculosis could be useful in developing and developed economies, and more generally where animals resistant to certain kinds of disease and harsh environmental conditions would be valuable.[277]

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[270] New York Times (26 November 2015) *Open season is seen in gene editing of animals*, available at: http://www.nytimes.com/2015/11/27/us/2015-11-27-us-animal-gene-editing.html?hp&action=click&pgtype=Homepage&clickSource=story-heading&module=photo-spot-region&region=top-news&WT.nav=top-news&_r=1; Reardon S (2016) Welcome to the CRISPR zoo *Nature* **531**(7593): 160-3; response to *Call for Evidence* by Compassion in World Farming.

[271] Ibid.; Wang X, Yu H, Lei A, *et al*. (2015) Generation of gene-modified goats targeting MSTN and FGF5 via zygote injection of CRISPR/Cas9 system *Scientific Reports* **5**: 13878.

[272] Cyranoski D (2015) Gene-edited 'micropigs' to be sold as pets *Nature* **526**(7571): 18.

[273] O'Neill J, *et al*.(2015) Antimicrobials in agriculture and the environment: reducing unnecessary use and waste (HM Government and Wellcome Trust commissioned report of the Review on Antimicrobial Resistance), available at: http://amr-review.org/sites/default/files/Antimicrobials%20in%20agriculture%20and%20the%20environment%20-%20Reducing%20unnecessary%20use%20and%20waste.pdf. The response to our *Call for Evidence* by Compassion in World Farming promotes a strategy for promoting 'positive health' in cattle through non-intensive farming methods. One element is to "Promote breeding for natural disease resistance and robustness and encourage a move away from genetic selection for high production levels as these appear to involve an increased risk of immunological problems and pathologies".

[274] Lillico SG, Proudfoot C, Carlson DF, *et al.* (2013) Live pigs produced from genome edited zygotes *Scientific Reports* **3**: 1-4.

[275] Ibid; The Guardian (23 June 2015) *Could these piglets become Britain's first commercially viable GM animals*, available at: https://www.theguardian.com/science/2015/jun/23/could-these-piglets-become-britains-first-commercially-viable-gm-animals.

[276] Reardon S (2016) Welcome to the CRISPR zoo *Nature* **531**(7593): 160-3.

[277] Research interview, Professor Hewinson, APHA.

5.27 Genome editing is of less interest in veterinary medicine than it is as a technique of cell-based therapy or gene therapy in humans; it is unlikely to be used for farmed livestock, although it may find a market among companion or show animals.

Moral and societal questions identified

5.28 Food production not only deals with one of the necessities of human life, but is also a matter of deep social significance, and one that is rooted in many characteristic cultural, ethnic, religious and social practices. Many of the questions relating to genomic manipulation of the foods that we eat are common to both plants and animals. They do not, however, simply invite empirical answers, however complicated but, rather, open up a complex of moral, political and scientific judgements. Those that surface as legal and regulatory questions, rest on conceptual distinctions (for example, between GMOs and non-GMOs), which, in turn, may be strongly imbued with moral and political judgements. They may involve attitudes to various factors such as how we value any potential harms and benefits to health associated with consuming animals, the environmental consequences of their diffusion, and the political and economic conditions of their production. From some perspectives 'genetic modification' seems less an empirical description than a moral designation, enshrined as a normative distinction. The use of genomic technologies and their consequences, however, must be seen in the context of possible alternatives: each has opportunity costs, with varying degrees of predictability, that involve people in collective acts of evaluation and moral reasoning, leading to societal choices that have further consequences for themselves and others.[278]

Confused terms

5.29 The sites and language of the discourse on genomic manipulation can be inaccessible to many interests and remote from consumers, both socially and geographically. Advanced biotechnology is predominantly a phenomenon of the rich world, although some of those most sensitive to its benefits and costs may be in the developing world. The technical language in which genomic manipulation is discussed by specialists in all disciplines (including both natural and social sciences) is frequently impenetrable to common understanding. This is a critical problem given the importance (acknowledged on all sides) of public engagement with biotechnology and food policy.[279] For example:

"Many people's concerns are, in fact, focused on the areas of scientific risk… However, as most people in the UK have not benefitted from a scientific education, they express concepts such [as] off-target and unexpected effects in less precise language. It is entirely unacceptable for any serious attempt to gauge public opinion and examine the ethical context of new scientific developments to dismiss the views of individuals who do not have the vocabulary to express themselves in scientifically-accurate terms."[280]

On the other hand, it is objected that:

> "One of the limitations faced by such a debate is that highly complex new science can rarely be explained in a soundbite, and this can be frustrating to the public and scientists alike, while providing an attractive area for campaign groups who can exploit public uncertainty."[281]

[278] Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.
[279] See, for example, Quinlan MM, Smith J, Layton R, *et al*. (2016) Experiences in engaging the public on biotechnology advances and regulation *Frontiers in Bioengineering and Biotechnology* **4**(3), doi: 10.3389/fbioe.2016.00003.
[280] Response to *Call for Evidence* by GM Freeze. From another perspective, Julian Hitchcock opines that "ethical debate is meaningless unless participants adopt a common language with shared, scientifically-informed, dispassionate meanings to key terms" (response to *Call for Evidence*).
[281] Response to *Call for Evidence* by the Agricultural Biotechnology Council.

5.30 To some extent different discourses make use of different lexicons: the public discourse may be filled with appeals to concepts of the natural and the artificial (and their analogues and cognates) which are found rarely, if at all, in the technical discourses (often because they are difficult to define in technical terms) although they are not without meaning.[282] Furthermore, terms that may seem superficially similar may have distinct meanings in different mouths.[283] The extent to which it is possible or necessary, for the effective governance of genome editing technologies, to present technical concepts in a way that non-specialists can understand and use, and whose responsibility it may be to make the concessions or efforts to achieve this understanding are moot points. However, meaningful political engagement depends upon finding a common language that is adequate to the presentation of a common problem rather than playing to a particular constituency.

Contested concepts

5.31 Perhaps the most contested concept in the vicinity of genome editing is that of the genetically modified organism (GMO).[284] The formal definition given in the relevant European Directive is conventionally glossed as the organism in question being produced using a particular kind of technique, especially one that inserts a transgene using recombinant DNA technology. The argument is put, particularly from the scientific research community, that genome-edited organisms should not be classified as GMOs where no transgene is involved, in which case the resulting organism is equivalent to one that could conceivably have arisen through conventional breeding techniques, without the inclusion of foreign DNA (from the use of a vector). In such cases, scientific analysis would, in principle, be unable to determine whether the characteristics of the organism had been produced by genome editing or by a 'traditional' breeding method.[285] In other words, the products of genome editing and 'traditional' breeding would in many cases be indistinguishable.

5.32 Others, nevertheless, assert that genome-edited organisms should be regulated as GMOs because the method of production is, in fact, one prescribed in the relevant Annex.[286] They base this claim on the alleged emphasis, in the European and (antecedent) Cartagena instruments, placed on "the use of in vitro techniques where the modification is induced by heritable material that has been prepared outside the organism" rather than the use of recombinant DNA technology specifically.[287] On this basis they argue that genome editing is significantly dissimilar to 'traditional' mutagenesis breeding so as to warrant more exacting regulation.

Inconsistent framings

5.33 What is at stake in the argument about whether food products developed using genome editing techniques are classified as GMOs is the kinds of enhanced regulatory scrutiny, political control, and marketing conditions (e.g. explicit labelling) that may be placed on particular instances of

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

[283] For example, the term 'traditional' (in the phrase 'traditional breeding techniques') can be a *faux ami*, being used within biotechnology discourse to designate breeding techniques that encompass the use of naturally-occurring or deliberately applied chemical mutagens and radiation in distinction from recombinant DNA technologies. "GE techniques are more precise than chemical or UV mutagenesis techniques, which have long been accepted as "traditional" approaches to breeding." (Response to *Call for Evidence* by BBSRC and MRC). This is at variance with the ordinary language meaning of 'tradition' as "A long-established custom or belief that has been passed on from one generation to another" (Oxford dictionaries).

[284] In their response to the *Call for Evidence*, the British Society of Plant Breeders expressed concern about the danger of genome editing being confused with transgenic (GMO) technology in public debate, which is largely 'political'. They paint an apocalyptic vision of our inability to meet global challenges of food security if genome editing technology were to be 'lost' as a result of this confusion (see below).

[285] This presents challenges for verifying traceability claims – see below.

[286] These others include Greenpeace – see response to *Call for Evidence*.

[287] Greenpeace "find that ODM [oligonucleotide directed mutagenesis] and SDN [site-directed nuclease] techniques fall into the category of direct modification using in vitro techniques, and hence would be classified as a GMO according to the EU and Cartagena definitions" (response to *Call for Evidence*).

food production.[288] This is non-trivial since, as discussed above, such measures may have a profoundly shaping effect on the agricultural biotechnology industry, the broader economy and the food supply.

5.34 At the heart of the regulatory system for food generally, and for GMOs especially – and this is common to almost all jurisdictions – is a concern, first and foremost, that the food should be safe for consumption. For prospective new products, this is established principally through an assessment of the risks it might pose to human health and wellbeing. Further considerations apply to risks to the health of animals and to the wider environment (for example, effects on biological diversity). In the case of novel products there is always some uncertainty and some room for dispute about what counts as relevant evidence. Accumulated evidence from the cultivation of genetically modified crops, however, has not demonstrated any exceptional risk to health.289 This has provided support to the increasingly frequent argument that GMOs should not be singled out for exceptional oversight but that all novel organisms should be assessed on the basis of their biological properties.[290] This means, essentially: on the basis of substantial equivalence to existing, well understood organisms.[291]

5.35 A reason for contemplating a move to product-based regulation is that there may be, in the future, products that are generated by the use of multiple techniques, which would present a challenge for classification on a process-based approach to regulation.[292]

> "The boundaries between established genetic modification (GM) and non-GM techniques will also become increasingly blurred as GE techniques develop. This raises questions about how organisms altered by any means should be regulated. Regulation based on the characteristics of novel organisms, however produced, would provide more effective, robust and future-proofed regulation than considerations based on the method used to generate them."[293]

5.36 A number of NGOs, nevertheless, continue to mount arguments for products developed by genome editing to be regulated as GMOs, and separately from other foods, on the basis of a putative risk to health or to the environment. This argument draws on claims about residual uncertainties: the uncertain effects on plant chemistry, biochemical pathways and unanticipated genomic interactions.[294] They suggest that biotechnology researchers are being misleading when they describe genome editing as 'precise' in order to emphasise its difference from first generation

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[288] Directive (EU) 2015/412 as regards the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory was passed essentially to unlock the impasse to GM approval at community level by providing Members States with further opportunities to control production in their territories.

[289] The most recent analysis is the NAS/NAM report, *Genetically engineered crops: experiences and prospects* (2016), available at: http://www.nap.edu/catalog/23395/genetically-engineered-crops-experiences-and-prospects?version=meter+at+null&module=meter-Links&pgtype=article&contentId=&mediaId=&referrer=https%3A%2F%2Fwww.google.co.uk&priority=true&action=click&contentCollection=meter-links-click.

[290] See: European Academies Science Advisory Council (2013) *Planting the future: opportunities and challenges for using crop genetic improvement technologies for sustainable agriculture*, available at: http://www.easac.eu/home/reports-and-statements/detail-view/article/planting-the.html. For the UK see: Biotechnology and Biological Sciences Research Council (2014) *New techniques for genetic crop improvement* , available at: http://www.bbsrc.ac.uk/web/FILES/Policies/genetic-crop-improvement-position-statement.pdf. For a further proposal, see: Huang, S, Weigel D, Beachy RN and Li J (2016) A proposed regulatory framework for genome-edited crops *Nature Genetics* **48**(2):109-11.

[291] "The question in this particular case is whether or not the familiarity that we have with the development of crops in which mutations and other small genetic alterations have been introduced in a blind manner, also applies for genome edited plants. Can we use that familiarity with the effects of classical mutagenesis? And does the way the conventional plant breeding sector develops, selects, evaluates, tests and registers new varieties also warrant enough safety for genome edited crops? Probably yes, because otherwise we would end up in situations where the same mutation has to go through a special legally binding registration process that requires a lot of testing when the mutation has been produced by genome editing, and none of this when the mutation has been achieved by conventional mutagenesis, or natural random mutagenesis (i.e. sunlight). This would be disproportionate and discriminatory." Response to *Call for Evidence* by the Vlaams Instituut voor Biotechnologie.

[292] Research interview with senior Monsanto officer.

[293] Response to our *Call for Evidence* from BBSRC and MRC.

[294] See response to *Call for Evidence* by Greenpeace.

GM: they point to the mistake of equating 'precision' in the ability to manipulate nucleotide sequence with precision in the prediction or control of consequences or in terms of gene function.[295] Biotechnology researchers typically respond to these claims by alleging that NGOs are overstating the risks and exploiting uncertainties for political ends.[296] They argue that the designation of products developed using genome editing is unnecessary given the equivalence to 'traditionally developed' products.

5.37 Although these arguments are ostensibly about risk, what is perhaps most at stake is how and, indeed, whether the framing of risk captures what is important to different people about the production of food using NBTs, and whether these differences may be reconciled.[297] In the first place, a risk assessment only seeks to quantify perceived risk; it does not in any way show how that risk – or any residual uncertainties – should be valued.[298] It is very likely, in fact, that they will be valued by different people, with different interests and expertise, in different ways. It is a reasonable complaint that risks of harm and potential benefits of genetically altered products are not treated commensurately (although it is less a matter of managing the balance of risks and potential benefits of any one technology as finding the optimum mix of technologies and approaches to the perceived challenges).[299] Furthermore, risk assessment only applies to those things that have been identified as hazards. Again, views may differ about priorities: whereas most people might be expected to include safety of foods as a high priority, attitudes to environmental impact may differ and be confounded by cognitive dissonance and adaptive preference formation (as may be seen in responses to climate change).[300] As well as being difficult to predict, some factors, such as systemic environmental effects, are difficult to quantify, may only become manifest in the long term, and may be resistant to rational appraisal, despite being potentially of high importance.

5.38 These factors may explain why, to the consternation of many in the biotechnology field, public opinion research continues to reveal a sizeable minority who are concerned about the risks of genetic modification.[301] Although genome-edited plants might be de facto analytically indistinguishable from traditionally bred ones, the fact that a "technical procedure, which might be perceived as unnatural, is involved in producing these new plants" may be of concern to some people.[302] This is arguably a matter for the consumers rather than producers, since it allows consumers to exercise choices about the kinds of producers and production systems they wish to support through their purchasing. On the other hand, lack of product differentiation through labelling may contribute to economic lock-in (e.g. a world in which there is no ketchup without GM tomatoes due to non-GM ketchup being outcompeted). An important question is therefore who decides what information consumers should be able to receive. If it is right that consumers should be able to make such a choice on grounds that they themselves choose, labelling may be particularly important in the case of products developed by genome editing just because of the

[295] See response to *Call for Evidence* by GM Freeze.
[296] Cf. response to *Call for Evidence* by the Agricultural Biotechnology Council.
[297] See also: Douglas M and Wildavsky A (1982) *Risk and culture. An essay on the selection of technological and environmental dangers* (Berkeley: University of California Press).
[298] For the distinction between risk and uncertainty see Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/. For a different understanding of risk see Stirling A (2007) Risk, precaution and science: towards a more constructive policy debate *EMBO reports* **8**(4): 309-15.
[299] "Public debate most often focuses on potential benefit, while risk is narrowly defined around quantifiable hazards to either health or the environment." Response to *Call for Evidence* by GM Freeze.
[300] Runciman D (2015) A tide of horseshit *London Review of Books* **37**(18): 34-6.
[301] "The 2014 Public attitudes to science survey found that most people do not feel informed about genetically modified (GM) crops and a sizable minority (28%) say the risks outweigh the benefits for GM crops." Ipsos MORI (2014) *Public attitudes to science* (available at: https://www.ipsos-mori.com/researchpublications/researcharchive/3357/Public-Attitudes-to-Science-2014.aspx). For the US, see Funk C, Rainie L, Smith A, *et al*. (2015): *Public and scientists' views on science and society*, Pew Research Center, available at: http://www.pewinternet.org/2015/01/29/public-and-scientists-views-on-science-and-society/.
[302] In Europe, perhaps the majority (cf. Lucht J (2015) Public acceptance of plant biotechnology and GM crops *Viruses* **7**(8): 4254-81, at page 4270). According to Araki and Ishii (2015), "some people will demand to know which food products are produced from genome-editing plants, regardless of the degree of genetic modification." Araki M and Ishii T (2015) Towards social acceptance of plant breeding by genome editing *Trends in Plant Science* **20**(3): 145-9, at page 148.

absence of any distinguishing traces of the use of the technique in the resulting product.[303] Consequently, tracing through an auditable chain of custody becomes indispensable for that purpose.[304]

5.39 At the cornerstone of risk management in Europe is the much-discussed precautionary principle. This is notoriously difficult to define and to apply. Arguably, its 'elasticity' has been exploited to exert political control over the agriculture industry.[305] This is particularly apparent in relation to the exploitation of the margin of uncertainty, which science cannot eliminate, and in the discontinuity between the descriptive discourse of science, and the normative discourse of regulation. (It is possible to give a scientific description of the similarities and differences between genetic engineering and genome editing technologies but science cannot prescribe whether those technologies should be treated together or distinctly in respect of how their products are labelled and how they are traded in a competitive marketplace. What science can speak of more meaningfully is the relative scientific risk associated with different approaches, which is why, in our 2003 report, *The use of GM crops in developing countries*, we defined a 'precautionary approach' as a response to overly conservative application of the precautionary principle. The report drew attention to the fact that any choice, including one to maintain the status quo, had a benefit and cost profile that should be appraised comparatively.[306]) It is perhaps the narrow use of the precautionary principle as a crude 'decision rule' (given that the EU does not have the competence to make political decisions that impinge on member states' sovereignty) that forces sceptics to continue to mount arguments based on the apparently diminishing uncertainties about health risks and environmental contamination. This impoverished discourse around scientific risk assessment, however, obscures the more significant arguments about commercial freedom and equity, securing public benefits, the nature of the food security challenge and the desirability of different future states of affairs.[307]

Contending imaginaries

5.40 The situation to which agricultural biotechnology offers a set of possible solutions has been presented as a significant global challenge. "The Food and Agriculture organisation estimates that we need to increase food production by as much as 70% in the next 35 years but notes that agriculture already uses 40% of earth's landmass, 70% of fresh water and employs 30% of the human population. Agriculture and forestry are responsible for over 30% of our carbon emissions. The potential for improving plants using genome-editing technologies is considerable."[308] Likewise, political constraints on the use of new breeding techniques have been presented as a threat: some of our respondents noted that GM debate had 'killed the GM industry in Europe'.[309] The potential 'loss' of genome editing-based technologies, through being conflated with transgenic (GMO) technology in public debate, invites a vision of redoubled global challenge: "If

[303] In the research interview with a senior Monsanto officer a distinction was made between identification and traceability: genome edited products may be traced, but not identified.

[304] The relevant law in the EU is Regulation (EC) 1830/2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms.

[305] References to the precautionary principle occur prominently (in Art.7) of the General Food Law Regulation and its application to GMOs is the whole purpose of Directive 2001/18/EC, which covers deliberate environmental release and placing on to the market of GMO products.

[306] This point was reiterated and expanded in *Emerging Biotechnologies* (2012) [recommendation 1 on consideration of counterfactuals and opportunity costs.] See: Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

[307] See Nuffield Council on Bioethics (2014) W*ritten evidence submitted 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).

[308] Cited in response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre.

[309] E.g. response to *Call for Evidence* by the British Society of Plant Breeders: "The GMO debate is clouded by political interests rather than remaining evidence-based, which has resulted in a *de facto* ban of GM in Europe and enhanced the global market power of breeding companies from outside the EU." They warn: "If it is decided that a European style GMO regulatory process must be applied to these products it will kill the potential for genome editing to be used to the benefit of European consumers."

genome editing is similarly lost, then all that remains to address the societal challenges of sustainable food production is classical breeding. This is unlikely to be sufficient to address the challenges of growing population, urbanisation and climate change."[310] However, an alternative framing suggests that this concern could betoken a premature or unwarranted hypothecation of societal and global challenges to particular technological solutions.[311] For example, responses to our Call For Evidence highlighted that intensification of food production was not the only available strategy to address global food security and that an equally substantial contribution could be made by tackling food waste or through revised farming practices and consumer preferences.[312] This draws attention to the need for an expanded framing that transforms more narrowly-defined 'problems' that invite technical solutions (in this case, problems of increasing food production and of reducing food waste) into potential components of a response to a broader societal challenge.

5.41 Expanding the parameters of the inquiry, however, also requires that attention be given to considerations that are both morally relevant and serve to lock-in particular technological pathways, such as the strong commercial and national economic interests involved.[313] The NBT platform has produced a fact sheet on the socio-economic impact of NBTs on the food supply chain in the EU that estimates that "a loss of 30% of the R&D in the EU would mean a loss in investment in high level equipment and jobs amounting to €210 million."[314] These interests sit starkly beside another important set of considerations that may be underrepresented in the discussion of global food security, namely the interests and agency of resource-poor communities, which are not natural markets for purely commercial products since the price of food there is necessarily low. Here, too, the impact of genome editing is potentially ambiguous and the response to it is a matter of political debate. "Just as government incentives are required for investment in neglected diseases that afflict developing countries, incentives may be needed to stimulate interest in the crops grown in these regions and in the growth of home-grown agri-tech ventures that can use genome editing technologies for the development of their own crops."[315]

5.42 Agricultural intensification appears to have significant momentum as a strategy for feeding the growing world population over the next 20 years or so, potentially bringing with it increasing susceptibility to infection and disease resistance.[316] Increasing dependency on biotechnology is itself a source of systemic vulnerability, with highly engineered products performing better in a controlled ecological niche but lacking robustness in response to environmental variation.[317]

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[310] Response to *Call for Evidence* by the BSPB. The response by the Agricultural Biotechnology Council cites Jack Bobo, former advisor at the U.S. Department of Agriculture, who has asserted that "the amount of food we need to produce in the next 40 years (is) equivalent to the same amount produced in the past 10,000 years." (Farmers Weekly (5 March 2013) *Food crisis will prompt GM foods rethink, says US aide*, available at: http://www.fwi.co.uk/arable/food-crisis-will-prompt-gm-foods-rethink-says-us-aide.htm. "What," they ask, "are the ethical considerations of not using gene editing technologies in plant science?"

[311] "The point of this scepticism is to draw attention to the error of committing prematurely to two sorts of potential frame: firstly, construing social 'challenges' as hypothecated to technological solutions (in general or particular) and therefore curtailing the exploration of other kinds of possible response; secondly, focusing the development of biotechnologies too tightly on solutions to particular challenges and therefore failing to be sensitive to the range of possible benefits they might bring, perhaps in radically different contexts." Nuffield Council on Bioethics (2012) *Emerging Biotechnologies: technology, choice and the public good* (London: Nuffield Council on Bioethics), available at: http://nuffieldbioethics.org/project/emerging-biotechnologies/.

[312] High Level Panel of Experts on Food Security and Nutrition (HLPE) (2014) *Food losses and waste in the context of sustainable food systems. A report by the High Level Panel of Experts on Food Security and Nutrition* , available at: http://www.fao.org/3/a-i3901e.pdf. Cited by response to *Call for Evidence* by Compassion in World Farming.

[313] "The European plant breeding industry is a world leader in terms of innovation, representing a market value of more around EUR 8,6 billion. Additionally, of the more than 7000 companies in the EU seed sector, a significant portion (in some Member States up to 90%) are Small-to-Medium-Size Enterprises (SMEs), which are widely recognised as a major driver of innovation and economic growth. Many of these companies depend on innovation and access to technology to remain competitive." Response to *Call for Evidence* by the Agricultural Biotechnology Council) citing International Seed Federation (2013) *Estimated value of the domestic seed market in selected countries for the year 2012* and European Parliament, Directorate General for Internal Policies (2013) *The EU seed and plant reproductive material market in perspective: a focus on companies and market shares*, available at: http://www.europarl.europa.eu/RegData/etudes/note/join/2013/513994/IPOL-AGRI_NT(2013)513994_EN.pdf.

[314] See: http://www.nbtplatform.org/background-documents/factsheets/fact-sheet---socio-economic-impact-of-nbts.pdf.

[315] Response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre.

[316] Research interview with Professor Hewinson (APHA).

[317] "Plants that are no longer capable of being an integral part of a biological system, that can no longer communicate and interact with beneficial soil organisms (eg mycorrhiza) except at a reduced level if at all, plants that require constant inputs to

Compassion in World Farming argue, for example, that genome editing might aggravate food insecurity if genome edited animals are used in industrial systems where animals are fed human-edible cereals and that contribute to environmental degradation.[318] What is presented as part of a solution may, they suggest, be a cause of the problem. Their vision, however, implicitly involves a move away from current levels of consumption of farmed meat and dairy products with perhaps unacceptable transition costs and deeply-rooted cultural resistance. The vision promoted by the UK's Royal Society, on the other hand, is one of 'sustainable intensification' that harnesses biotechnologies to address the multiple constraints of increasing population, water shortages, degradation of farmland and climate change.[319]

Box 5.1: Genome editing for PRRS

Porcine Respiratory and Reproductive Syndrome (PRRS) is a potentially devastating disease that threatens intensive pig production (the largest US facilities have barns housing up to 10,000 sows each). PPRS a causes significant reproductive loss in pigs and can move rapidly through a herd.[320] PRRS itself costs between 5% and 15% of production in any given year, since the disease is currently not well controlled and this means that affordability is impacted, both in terms of the product and the cost of corn previously fed to the infected animals.[321] The standard disease management protocol is the slaughter of exposed animals resulting in severe economic losses to the producer (or their insurer).

PRRS resistance is a recessive trait and not a readily observed phenotype (understandably so, given the standard disease management protocol). At least two major companies (Cibus and Genus) have research programmes using genome editing to engineer resistance to PRRS in order to improve the welfare of intensively farmed animals by reducing their risk of disease and reduce the economic risk to farmers. Genus quantitatively monitor more than 20 individual traits in pigs, all of which matter to their commercial performance, including feed conversion, efficiency, litter size, health and robustness (as a negative effect of genetic alteration represented by changes to these other traits might outweigh the benefits of PRRS resistance).[322]

The health of intensively farmed animals is a major area of concern. A pig may end up in receipt of, for example, 15 vaccinations in a very short life and the animal's immune system may not anyway be able to respond effectively. Intensive husbandry systems may contribute to pathogen emergence and evolution.[323] Research into the variable susceptibility of different breeds of pigs to viruses suggests that some level of resistance might be developed through breeding but it is likely in most cases that the pathogen would quite quickly adapt to the new strain.[324]

International projects in developing countries on intensification of pig production may compound both animal health problems and social inequalities. It is now better appreciated that subsistence farming plays a key role as part of an integrated farming system, also directly benefitting poorer farmers, and that there are also disease control benefits from this kind of farming. Other drivers for de-intensification relate to fostering development and sustainable global food production by focussing on improving the circumstances of poor farmers in the developing world.[325]

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the detriment of soil, pollinators, insects, biodiversity, healthy and ecologically sustainable agricultural systems – these are not the answer to current perceived and/or real problems. We need a different mindset that sees the interactions within ecosystems as the primary concern." Response to *Call for Evidence* by EcoNexus.

318 Response to *Call for Evidence* by Compassion in World Farming.

319 "As highlighted in the Royal Society report, *Reaping the benefits*, the pressures of soil degradation, water shortages and climate change are going to put pressure on crop plants and production will need to be sustainably intensified […]. Genetic techniques could also be used to introduce radical and highly significant improvements to crops for example: increasing photosynthetic efficiency, reducing the need for nitrogen or other fertilisers and changing annual plants to perennials." But: "Genetic technologies are not a 'silver bullet' and they will need to be combined with other expertise, for example agronomy to support crop production." Response to *Call for Evidence* by the Royal Society.

320 Research Interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus.

321 Research Interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus.

322 Research Interview with Jonathan Lightner, Chief R&D and Scientific Officer at Genus. See also: Whitworth KM, Rowland RRR, Ewen CL et al. (2016) Gene-edited pigs are protected from porcine reproductive and respiratory syndrome virus, *Nature Biotechnology* **34**(1): 20-22.

323 Research interview with Professor Drew (APHA) citing Drew, TW (2011) The emergence and evolution of swine viral diseases: to what extent have husbandry systems and global trade contributed to their distribution and diversity? *Revue scientifique et technique (International Office of Epizootics)* **30**(1): 95-106.

324 Research interview with Professor Drew, citing Ait-Ali T, Wilson AD, Westcott DG, *et al*. (2007) Innate immune responses to replication of porcine reproductive and respiratory syndrome virus in isolated swine alveolar macrophages *Viral Immunology* **20**(1): 105-18.

325 Research interview with Professors Drew and Hewinson (APHA).

5.43 One of the acknowledged challenges in identifying the appropriate frame for addressing societal challenges, such as food production, and expanding beyond a linear relation between a narrowly defined problem and a privileged solution, is to locate a suitable space of engagement in which different perspectives and knowledge may encounter each other. This requires allowing the political into the debate about biotechnologies, rather than seeking to resolve it on narrowly scientific grounds. "A recent John Innes Centre public dialogue project highlighted that the public was keen that scientists should consider the wider context of a problem, such as economic, societal and political factors which could be affecting food security, and take part in wider discussions on these lines."[326] This requires both openness and good will on all sides, and an orientation towards an agreed definition of the common challenge.[327]

Conclusion

5.44 Our objective in this interim report is to identify the distinctive moral questions, if any, raised by developments in genome editing, to consider the proper way of posing these questions (and, in doing so, to suggest how they might be addressed), and to prioritise these questions for the ethical deliberation that will follow in subsequent initiatives.

5.45 Many of the issues, such as animal welfare and the virtues or necessity of intensive agricultural systems, are not peculiar to genome editing, although developments in genome editing may bring additional factors into consideration or change the parameters of debate. Genome editing has quickly added another focus to these continuing debates. As a young technology, still undergoing continual technical refinement and exploring its potentialities, genome editing may appear to be drawn in as a vulnerable neophyte to abstruse and militant political debates. By changing the focus, however, genome editing may also insert a critical reflection into these debates, by challenging their parameters (introducing new future visions) and assumptions (such as the significance of the GMO/non-GMO disjunction), calling forth new evaluative frameworks and comparative analyses.

5.46 In relation to genome editing as a technique in food production, many of the questions have to do with classification boundaries – not so much where genome editing fits within existing boundaries but about the fitness of the boundaries, in relation to their underlying rationales, with consequences for regulation, labelling and public acceptance. Our general conclusion about framing ethical questions around genome editing seems appropriate in this instance too, namely, that the approach to normative questions – the approach that we should take in the second part of this project – should be to approach these questions from the point of view of the societal challenge on which genome editing has a potentially transformative impact, rather than the technological development itself. It is claimed that there is a need for harmonisation not only of regulatory controls but of ethical approaches.[328] By hypothesis, harmonisation of regulation may not be possible without harmonisation of ethical approaches. This leads to a second conclusion: that there is an outstanding question about the proper jurisdiction for both. The assumption that this jurisdiction, and its corresponding 'public', is that of the nation state or the regional bloc is therefore a question that requires further interrogation.

[326] Response to *Call for Evidence* by the Sainsbury Laboratory and John Innes Centre.

[327] The response from the Sainsbury Laboratory and John Innes Centre to our *Call for Evidence* contained a passage that could serve as a creed for engaged bioscientists: "It is important that scientists are seen as individuals not as a white-coated 'other'. We should represent ourselves as members of the community and our motivations and desire to achieve positive social outcomes should be communicated often and clearly. We should seek to describe the technologies that we employ in terms that are open and transparent, and should be clear about the relative similarity between plants with mutations induced by genome- editing technologies, those produced using older technologies and those that have acquired mutations without human intervention. Scientists should be sensitive to the role of food in human culture and religion and respect the beliefs of those that differ from our own while also speaking to the ethical need to produce sufficient nutritious food for our growing population." The same sentiment ought to apply, mutatis mutandis, to NGOs and to other actors within this public space.

[328] Response to *Call for Evidence* by the Vlaams Instituut voor Biotechnologie.