Royal Society of Biology response to Defra consultation on the regulation of genetic technologies

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The Royal Society of Biology (RSB) is a single unified voice, representing a diverse membership of individuals, learned societies and other organisations. We are committed to ensuring that we provide Government and other policymakers, including funders of biological education and research, with a distinct point of access to authoritative, independent, and evidence-based opinion, representative of the widest range of bioscience disciplines.

The Society welcomes the opportunity to respond to Defra regarding the regulation of genetic technologies. We are pleased to offer these comments, which have been informed by specific input from our members and Member Organisations across the biological disciplines. Our Member Organisations are listed in Appendix 2.

Summary
- In order to protect ecosystems and reduce biodiversity loss, agriculture must do more with less, while adapting to rising global demand and changing climates. No single development can address these complex challenges, and we will need to use all the tools available to deliver the world we need for human survival in acceptable quality conditions.

- Genome editing (GE) offers many potential benefits to society, but these benefits cannot be delivered currently, as genome edited organisms are regulated as GMOs.

- No clear criteria can be described that would determine whether an organism produced by genome editing could have been produced by traditional breeding. This means no clarity can be achieved using this principle, and we would not recommend using it as the basis for regulation.

- A modern regulatory system should adopt a proportionate and science-based approach to risk-assessment. This would entail assessing new products by their characteristics and potential impacts, enabling a single approach to all forms of breeding. It would be flexible and adaptive to incorporate future methodological developments and emerging policy objectives.

- In plant breeding, it is widely recognised that harmful unintended effects are no more likely to arise through GE than through traditional methods of plant breeding, which often employ chemical based mutagenesis leading to wide genomic disruption. In animal breeding, genome editing is a fast evolving technology that can refine and expand current breeding practices, for example by introducing *de novo* favourable alleles. However, genome editing can still lead to unwanted artefacts that must be carefully checked for with appropriate validation strategies.

- Experience from the introduction of GMOs in the 1990s indicates that changes to food products made without the informed agreement of consumers are likely to be met with resistance and rejection, even when scientists and regulators are satisfied with their safety. Public support is essential to realising the benefits of genome editing. A broad public dialogue is necessary, in which clarity and transparency will be essential to obtain and maintain trust.

- Enabling UK farmers to grow genome edited products could help them to compete with those in other parts of the world where these methods are already used commercially. However, it may equally exclude markets, depending on the regulatory requirements of the trading partner country in question. The rules around exporting genome edited products and any risk to trade, particularly with the EU, will need to be thoroughly assessed and communicated.

- There is broad consensus in our membership that certain products developed using genetic technologies need a streamlined regulatory approval process within scope of existing non-GMO legislation.

- We propose a pragmatic, phased and enabling approach to regulatory reform consisting of an early phase of adaptation of the current legislation followed by a transition to a new regulatory regime. We list a number of desirable principles for designing new regulations in answer to question 6. These include: a balanced assessment of expected benefits and any emerging risks; a focus on policy objectives and associated protection goals; the importance of global alignment and responsible pathways to innovation; and the inclusion of principles of flexibility, adaptability and proportionality.

List of abbreviations:

ACNFP: Advisory Committee on Novel Food and Processes
ACRE: Advisory Committee on Releases to the Environment
ART: Assisted Reproductive Technologies
CA: Codex Alimentarius
CRISPR: Clustered Regularly Interspaced Short Palindromic Repeats
EFSA: European Food Safety Authority
FAO: Food and Agriculture Organization
FSA: Food Standards Agency
GE: Genome Editing or Genome Edited
GM: Genetic Modification

GMO: Genetically Modified Organism
HDR: Homology-directed repair
HR: Homologous recombination
NHEJ: Non-homologous end joining
OECD: Organisation for Economic Co-operation and Development
SDN: Site-Directed Nuclease
TALEN: Transcription Activator-Like Effector Nuclease
WHO: World Health Organisation
ZNF: Zinc Finger Nuclease

PART 1: THE REGULATION OF GMOS WHICH COULD HAVE BEEN DEVELOPED USING TRADITIONAL BREEDING METHODS

This part of the consultation addresses the regulation of GMOs produced by gene editing (GE), or other genetic technologies, but which could have been developed using traditional breeding methods.

1.

Currently, organisms developed using genetic technologies such as GE are regulated as genetically modified organisms (GMOs) even if their genetic change(s) could have been produced through traditional breeding.

Do you agree with this?

~~**Yes – they should continue to be regulated as a GMO**~~

No – they should not continue to be regulated as a GMO

Please explain your answer, providing specific evidence where appropriate. This may include suggestions for an alternative regulatory approach.

Shortcomings of current GMO regulation

1.1   Current GMO regulation, derived from the legal framework established by the European Union, has tightly (and often unduly) restricted the use of GMOs. The regulations, as they have been implemented, are both inefficient and disproportionate.

1.2   Under EU GM regulations, product developers must compare a new GM product with a suitable non-GM comparator for an expanding (and potentially unlimited) set of characteristics. The biological relevance of any differences in these characteristics must then be evaluated, but the extent of any differences that should be deemed acceptable is not defined. This approach can result in the production of huge amounts of data that require significant effort from regulators to evaluate. The data requirements are disproportionate to the risks being assessed, and time and costs involved in undergoing assessment are prohibitive to the development of new products.

1.3   Genome editing is a tool which holds promise and, if appropriately managed, offers a route to achieving many potential and much needed benefits to society. These benefits could span a wide range of areas, from food security and waste management through to drug development, and would arise from the development of new varieties of plants and animals. Such varieties are currently not allowed to be cultivated for commercial purposes in the UK because they are regulated as GMOs. Creating a regulatory framework in which products of

genome editing are not regulated in the way that GMOs currently are, is key to realising these benefits.

<u>Regulation of products rather than processes</u>

1.4   In traditional breeding (see response to Question 4), mutations of many kinds are known to occur, creating variation that provides the basis for improvement. While in traditional breeding, neither the nature of these mutations nor the regions of the genome in which they occur are controlled, by using genome editing, breeders can induce mutations in a precise, targeted way, thereby obtaining a desired result far more quickly.

1.5   Whether a mutation is achieved by traditional methods or by genome editing has no bearing on the safety of the final product. Nor is the size of a genetic change necessarily related to the magnitude of the effect on the product. It is the characteristics of this final product, not the method by which the mutations are produced, that is relevant in decisions about safe use.

1.6   A proportionate, science-based regulatory system would assess new products by their characteristics, considering the particular traits of a product. Traits with an established history of safe use need not undergo extensive assessment, whereas a novel trait introduced to an organism would trigger a more extensive risk assessment, where this could have an environmental impact or lead to accumulation of a potential allergen, for example. As well as safety for people and the environment, assessment of novel traits should consider potential ethical and social effects, and implications for animal welfare.

1.7   All forms of breeding have the same goal: to manipulate the genome of an organism to produce a variant with new, desired characteristics. A regulatory system that assesses the characteristics of a product would enable a single approach to all forms of breeding, and could be flexible so that it could incorporate future methodological developments.

1.8   An attempt to design a system in which the methods used in breeding trigger different levels of risk assessment would rest on the faulty premise that the different methods create different levels or risk. Further, it would quickly become mired in difficulty, as clear delineations between what is achieved by 'traditional breeding' and other forms of breeding are far from simple.

1.9   Traditional breeding involving mutagenesis, which has a long history of safe use in plant breeding, can induce many kinds of significant changes in the genomes of new organisms. For many crop plants, it is possible to move genes between closely related species using traditional breeding methods. Meanwhile, changes to the genome using genome editing methods may be impossible to detect.

1.10   In animal breeding, genetic improvement via traditional breeding programmes is limited by the variation that exists in elite populations and it is difficult to bring in new traits via cross-breeding without diluting the genetic merit of the ensuing progeny, which would require generations of back-crossing to resolve. Genome editing permits precise alteration of single or multiple base pairs in the genome of animals, therefore it allows the introgression of

favourable alleles derived from populations for which cross-breeding would be impractical or impossible; it even allows the rational design of novel alleles.[1] This can be achieved in a single generation without dilution of genetic merit. Additionally, current domestic breeding pools often utilise a tiny fraction of the genetic variation available in that species. Wild relatives are a source of key alleles to future-proof agriculture (in the face of changing climatic conditions, for example) and resequencing projects are identifying the function of allelic differences. Beneficial 'wild' alleles can now be incorporated directly into elite germplasm via allele replacement or by recreating mutations using gene editing. This genetic 'rewilding' application could help to reduce genetic erosion and safeguard the genetic diversity of farmed and domesticated animals.[2] It should be noted that, at the herd-level, a general improvement in the health and welfare of domestic species may come alongside an increase in the genetic diversity of domestic livestock populations.[3]

1.11 Several of our members have suggested some immediate short term amendments that could be achieved with the inherited EU legislation, which Defra might consider, while reviewing broader changes to the regulatory framework. One possible short term amendment would be to adopt in the UK the Cartagena Biosafety Protocol (CBP) definition for GMO (Otherwise known as LMO, "living modified organism"), based on the "novel combination of genetic material". This change could make it easier, for example, to exclude products of genome editing from the inherited legislation that do not involve extraneous DNA. Along similar lines, certain forms of genome editing that are considered not to result in genetic modification could be added to a list of exclusions (based on Annex 1A part 2 of the Directive 2001/18/EC[4]). In certain circumstances, the UK could consider invoking "differentiated procedures" under Article 7 of the EU GMO Directive 2001/18/EC, which enable certain GMOs or other products of gene technology to be subject to simplified procedures thereby having a much lighter "regulatory" touch. Other items of inherited law are also important (for example, Regulation 1829/2003 and Regulation 503/2013). Defra might wish to consider the use of Article 5, Regulation (EC) 503/2013, which allows for a derogation from the need to do studies, if scientifically justified. This could ease the burden of burden from developers of providing large amounts of information during risk assessment.

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[1] Lillico, S. (2019). Agricultural applications of genome editing in farmed animals. Transgenic Res 28(Suppl 2): 57. https://doi.org/10.1007/s11248-019-00134-5

[2] For a discussion about the use of modern biotechnologies for the reintroduction of properties of wild species in the context of crop production and their bearings on organic farming please see Marchman Andersen, M. et al. (2015). Feasibility of new breeding techniques for organic farming. Trends in Plant Science, Vol. 20, No.7. https://doi.org/10.1016/j.tplants.2015.04.011. For the potential introgression of valuable alleles from wild ancestors and extant congeners of farmed animals please see Rexroad, C., et al. (2019). Genome to Phenome: Improving Animal Health, Production, and Well-Being – A New USDA Blueprint for Animal Genome Research 2018–2027. Frontiers in Genetics, 10:327. doi: 10.3389/fgene.2019.00327

[3] Regarding the importance of genetic diversity for the ability of farmed animals to adapt to environmental challenges please see the collections of studies 'Advances in farm animal genomic resources' available online here https://www.frontiersin.org/research-topics/2123/advances-in-farm-animal-genomic-resources

[4] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms. https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:32001L0018

The need for products of agricultural biotechnology

1.12   The UN Food and Agriculture Organisation (FAO) estimates that between 20 and 40 percent of global crop production each year is lost to pests, with plant diseases costing the global economy around $220 billion annually, and invasive insects around US$70 billion.[5]

1.13   Genome editing has been used to develop wheat with resistance to a major fungal disease, powdery mildew, which could reduce the need for pesticide applications;[6] it has also been used to generate pigs that are resistant to the Porcine Reproductive and Respiratory Syndrome Virus (PRRSV), a highly infectious virus which causes pig disease and mortality, with a £2bn worldwide cost to the food industry.[7] Recently, researchers have used genome editing to develop a line of the Cavendish banana resistant to Panama disease tropical race 4 (TR4).[8] Examples such as these show some of the potential benefits to the UK and globally that are possible using genome editing, through reducing the need for pesticide applications, improving animal health and welfare, and making the advances needed to feed the growing global population through sustainable use of land and resources. Such advances would improve food security, and increase efficiency in agriculture, helping to ensure an affordable food supply, while reducing the environmental cost of production. Further examples of applications of genome editing may be found in our response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals',[9] and our report on plant science, Growing the Future.[10]

1.14   Agriculture must produce sufficient, nutritious and safe food – along with fuels, fibres and other products – while reducing its environmental footprint. This must be achieved amid generally rising global demand, changing climates, the need to protect our ecosystems to reduce biodiversity loss, and the increasing spread of pests and pathogens - all without compromising, and ideally while improving quality and animal welfare. No single development can address these complex challenges, and we will need to use all the tools available to deliver the world we need for human survival in acceptable quality conditions.

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[5] FAO, 2019. New standards to curb the global spread of plant pests and diseases.

[6] Zhang et al., 2017. Simultaneous modification of three homoeologs of TaEDR1 by genome editing enhances powdery mildew resistance in wheat.

[7] Burkard C., et al., 2017. Precision engineering for PRRSV resistance in pigs: Macrophages from genome edited pigs lacking CD163 SRCR5 domain are fully resistant to both PRRSV genotypes while maintaining biological function.

[8] Queensland University of Technology (QUT), 2021. QUT Panama disease breakthrough sparks US funding

[9] Royal Society of Biology, 2019. Royal Society of Biology response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals'

[10] Royal Society of Biology, 2019. Growing the Future.

2.

Do organisms produced by GE or other genetic technologies pose a similar, lesser or greater risk of harm to human health or the environment compared with their traditionally bred counterparts as a result of how they were produced?
Please provide evidence to support your response including details of the genetic technology, the specific risks and why they do or do not differ. Please also state which applications/areas your answer relates to (for example: does it apply to the cultivation of crop plants, breeding of farmed animals, human food, animal feed, human and veterinary medicines, other applications/ areas).

2.1   In the context of risk assessment, risk can be defined as the severity of a hazard multiplied by its probability of occurrence.[11] Overall GE/GM organisms present similar risks to traditionally bred counterparts but risks could be lesser or greater depending on the product under consideration.

2.2   Before we discuss whether the way GE organisms are produced pose additional risks, it is important to stress that a future risk assessment for GE/GM organisms should not be triggered by the techniques used in generating the organisms but should incorporate a number of factors, according to the product and in a proportionate manner, such as: the specific attributes of the product assessed, its intended use, considerations of the product development process, and the context in which the impacts are expected (e.g. in relation to human food and animal feed, to the environment or to animal health and welfare). To facilitate the discussion, we will distinguish plant and animal breeding in our response, while acknowledging that additional considerations might apply to GE/GM microorganisms according to their uses. In answer to question 5, we will consider the merit of having an integrated, stepwise, case-by-case approach to risk assessment as part of a future regulatory framework.

2.3   When considering the method of production, we must recognise that technologies are still evolving and new potential applications are developed continuously. Furthermore, the emergence of new risks associated with GE and other technologies must be judged relative to other breeding methods and may vary according to the organisms, the details of the technology and the complexity of the targeted modification to be realised – "the efficiency and specificity of genomic alterations depend not only on the properties of the genome-editing system introduced into cells but also on the characteristics of the cellular repair mechanisms (NHEJ versus HDR)".[12]

2.4   The unintended changes described below may not necessarily represent a hazard to human health or the environment in all cases (i.e. lead to riskier products or harmful phenotypes). Nonetheless they should be carefully assessed and eliminated during product development, if the intended genomic change is to be achieved.

2.5   From a technological standpoint, unintended genomic changes, both at the targeted site (on-target) or away from it (off-target), could be judged to represent potential hazards.[13]

2.6   Off-target effects. GE tools can introduce changes in sequences at risk sites away from the target sequence of interest. However, a reduction of the frequency of these off-target changes, and our

[11] Hull, R. et al., 2021. Genetically Modified Plants - Assessing Safety and Managing Risk (2nd Edition). Please see chapter 4.
[12] NAM/NAS/RS, 2020. Heritable human genome editing - International Commission on the Clinical Use of Human Germline Genome Editing
[13] Burgio, G. et al. (2020). Anticipating and Identifying Collateral Damage in Genome Editing.

ability to detect them, has progressed in recent years and their occurrence rate can be below 0.01% at individual at-risk sites in some cases.[14] Careful molecular design, the use of bioinformatics tools to predict off-target at-risk sites and, importantly, detection assays using targeted deep sequencing to identify actual cleavage sites, all allow us to manage and control for off-target effects. Furthermore, once identified these types of unwanted changes can be bred out using standard breeding strategies,[15] unless the off-target region is in linkage disequilibrium with the target site.

2.7   On-target effects. These unwanted changes can take many forms: "single nucleotide variations, indels, large and/or complex genomic rearrangements, segmental duplications, chromosomal translocation, terminal chromosomal truncation up to several megabases, or loss of one or both arms of a chromosome".[16] If applied in early embryos, the kinetics of double strand breaks and repair mechanisms can translate into mosaicism of the mutated alleles.[17]

2.8   Additional unwanted effects. The co-delivery of donor DNA (repair template or vector for nuclease delivery) can yield ectopic insertions of unwanted sequences. A recent example is the introgression of a plasmid gene in the genome of GE cattle, which was not identified in the first analysis of the animals.[18,19] Conventional methods based on PCR and Sanger sequencing must be properly adapted and supplemented with other molecular assays in order to capture the ectopic insertion of donor DNA.

2.9   A recent review provides an overview of the current challenges of anticipating and identifying collateral damage in genome editing.[20] It also states that no single assay can capture all the potential outcomes of genome editing therefore "defining the appropriate validation strategy will determine the best possible combination of assays in terms of their scope and available resources, and requires the anticipation of potential outcome, genetic complexity of the edited material, and essential quality criteria for a given application".[21] The improvement of efficiency and accuracy of the technologies coupled with an improved understanding of the mechanisms of repair and appropriate assays to evaluate the correctness of the resulting genome-editing event will effectively manage these issues.

2.10   We will now discuss how these potential hazards might lead to additional risks in plant and animal breeding in comparison with traditionally bred counterparts.

2.11   In plant breeding, it is widely recognised that harmful unintended effects are no more likely to arise through GE than through traditional methods of plant breeding, which often employ chemical or radiation based mutagenesis leading to wide genomic disruption. Risks from the use of GE may therefore be similar, or indeed lesser (see Table 1 below). Using existing breeding practices as the baseline, it can be concluded that the processes associated with GE are safe – a conclusion also reached by the EFSA panel on genetically modified organisms.[22] When considering the methods of production, the potential hazards associated with GE techniques are:

[14] NAM/NAS/RS 2020. Op.cit. (see footnote 12)

[15] Young, A.E., et al. (2020). Genomic and phenotypic analyses of six offspring of a genome-edited hornless bull.

[16] Burgio, G. et al. (2020). Op.cit. (see footnote 13).

[17] Mianné, F. et al. (2017). Analysing the outcome of CRISPR-aided genome editing in embryos: Screening, genotyping and quality control.

[18] Regalado, A. (2019). Gene-edited cattle have a major screwup in their DNA.

[19] Young, A.E. et al. 2020 author correction

[20] Burgio, G. et al. (2020). Op.cit. (see footnote 13).

[21] Burgio, G. et al. (2020). Op.cit. (see footnote 13).

[22] EFSA Panel on Genetically Modified Organisms (EFSA GMO Panel), 2020. Applicability of the EFSA Opinion on site-directed nucleases type 3 for the safety assessment of plants developed using site-directed nucleases type 1 and 2 and oligonucleotide-directed mutagenesis

a. The need for introduction of GE constructs into totipotent cells (e.g. protoplasts, meristematic tissue) that have to be regenerated to produce complete plants. The regeneration process can result in somaclonal variation. This can be controlled in subsequent selection and breeding steps.

b. If transformation is needed, unwanted sequences might be integrated into the host genome even if the GE material is incorporated at targeted site(s) by NHEJ or HR. The EFSA GMO panel indicated that: "if the final product is not intended to retain any exogenous DNA, the applicant should assess the potential presence of a DNA sequence derived from the methods used to generate the SDN modification (e.g. plasmids or vectors, following the indication in Section 3.1.3 on methods for delivering the genome editors in plants)".[23]

c. "Off-target" effects which are specifically noticeable in ZNFs and some CRISPR procedures[24,25]. There are various ways of predicting these effects in CRISPR[26] and of reducing them[27,28]. The EFSA GMO panel recently concluded that: "number of off-target mutations generated by SDN-based methods is lower than the number of mutations observed in conventional breeding due to spontaneous or induced mutations and [..] that the analysis of potential off-targets would be of very limited value for the risk assessment".[29] This is summarised in the table below:

Table 1: Examples of risk of GE compared with traditional breeding (TB)

Hazard	Probability in GE	Risk	Comment
Possibility of non-target mutation	Low	Low	Random mutation in TB
Unwanted genes introduced	Low/high	Low/high	High in SDN-3
Fault in gene expression	Low	Low	Gene targeted in GE
Fault in heritability	Low	Low	GE provides material for TB

d. Importantly, we note that "backcrossing following the transformation process can be used to remove these potential off-target mutations from the final product, except for those that are genetically linked to the intentionally modified locus".[30]

e. Overall, GE approaches represent an improvement over traditional breeding methods both when considering the process (see table above) and certainly when seen from a

[23] EFSA Panel on Genetically Modified Organisms (EFSA GMO Panel), 2020. Op. cit (see footnote 22)

[24] Hendel, A., et al. (2015). Quantifying on and off-target genome editing. Trends Biotechnol.

[25] Modrzejewski et al., 2020. Which Factors Affect the Occurrence of Off-Target Effects Caused by the Use of CRISPR/Cas: A Systematic Review in Plants.

[26] Kang, SH., et al. (2020). Prediction-based highly sensitive CRISPR off-target validation using target-specific DNA enrichment.

[27] Chen, SJ (2019). Minimizing off-target effects in CRISPR-Cas9 genome editing.

[28] Naeem et al., (2020). Latest developed strategies to minimize the off-target effects of CRISPR-Cas-mediated genome editing.

[29] EFSA Panel on Genetically Modified Organisms (EFSA GMO Panel), 2020. Op. cit (see footnote 22)

[30] EFSA Panel on Genetically Modified Organisms (EFSA GMO Panel), 2020. Op. cit (see footnote 22)

product standpoint (as discussed in answers to other questions). Overall, GE plants do not raise additional specific risks to human health or the environment relative to traditional counterparts, which cannot be carefully managed within a proportionate and agile risk assessment, should a specific hazard be identified (e.g. potential for ectopic introduction of unwanted DNA sequences).

2.12   In animal breeding, the technical constraints described above are pertinent and despite the fact that CRISPR/Cas9 made genome editing easier and more accessible, its use can still lead to unwanted artefacts that must be carefully checked for. As described in the literature, there are a number of factors that should be assessed when validating GE outcomes and an array of techniques to do so.[31]

2.13   We discussed current limitations of the GE technology in farmed animals in a previous response to a consultation by the Nuffield Council on Bioethics[32] - some of which do not depend on the molecular mechanisms of the genome editing but on the use of specific assisted reproductive technologies as part of a GE project (as mentioned in our answer to question 3 below). We did not identify additional risks to human health and the environment specifically due to the techniques, but we raised important considerations for animal welfare. In relation to environmental risks, the creation of GE sterile fish - a germ cell-free salmon is an interesting case study[33] - provides an opportunity to reduce the risk that GE fish might escape from open-sea cages, interbreed and pass edited alleles on to wild stocks.[34] Another factor to consider is how the techniques will be integrated in wider scale breeding programmes.[35] It may also be important to consider cumulative effects, as the introduction of multiple edits simultaneously into broodstock animals might be required to target multiple traits, or multiple causative alleles for the same trait. As stated in a recent paper, "thorough testing of edited animals is required to assess and exclude possibilities of unintended and potential detrimental pleiotropic effects of edits before any application in production".[36] In all cases, comprehensive screening of founder livestock is important to maintain public trust and political support in the technology. Furthermore, "information obtained with genetically edited founder animals (likely to be mosaic) must be interpreted on the basis of the intrinsic genetic complexity of these animals and the genetic content of progeny must be extensively revalidated"[37].

2.14   As discussed further in answer to Question 5, we agree that "while process-based considerations and characterization of genome level effects may prove somewhat useful in the problem formulation for a given case of genome editing, the nature of the derived product would seem the stronger focus for any subsequent risk/safety assessment which may be

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[31] Burgio, G. et al. (2020). Op.cit. (see footnote 13).

[32] Royal Society of Biology, 2019. Royal Society of Biology response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals'

[33] Kleppe, L. et al. (2017). Sex steroid production associated with puberty is absent in germ cell-free salmon.

[34] Gratacap, RL et al. (2019). Potential of Genome Editing to Improve Aquaculture Breeding and Production.

[35] Tait-Burkard, C. et al. (2018). Livestock 2.0 – genome editing for fitter, healthier, and more productive farmed animals.

[36] Gratacap, RL et al. (2019). Op.cit. (see footnote 34)

[37] Burgio, G. et al. (2020). Op.cit. (see footnote 13). See page 908 for quote

conducted".[38] It could be advantageous for a reformed regulatory framework to adapt the requirements for risk assessment to the specific cases (organisms, products etc.) and applications in a proportional, agile and stepwise manner.

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[38] Wolt, J. (2019). Current risk assessment approaches for environmental and food and feed safety assessment.

3.

Are there any non-safety issues to consider (e.g. impacts on trade, consumer choice, intellectual property, regulatory, animal welfare or others), if organisms produced by GE or other genetic technologies, which could have been produced naturally or through traditional breeding methods, were not regulated as GMOs?

[Yes/~~No~~]

Please provide evidence to support your response and expand on what these non-safety issues are.

Clear aims and goals for agricultural policy

3.1   With any significant technological change come economic, environmental and social impacts. In the case of genome editing, there are important questions about who wins and who loses. For example, considering commercial markets, while genome editing has great potential benefits, there may be new advantages and disadvantages for competitors in the relevant product sector.

3.2   In the development of regulation, it would be helpful to clarify the priorities for our food production system. These aims should fit with Government policy commitments and key targets and standards nationally and internationally, such as those in the UN Sustainable Development Goals, the Government's 25 Year Environment Plan, and the National Food Strategy.

3.3   From these aims, a set of specific goals could be developed based on the wider societal values regarding human and animal health, plant and soil health, biodiversity and rural communities. These goals, agreed by policymakers in consultation with scientists, stakeholders and the public, would provide a reference for researchers, product developers, regulators and farmers, to enable the development and deployment of solutions in agricultural technology that are aligned with society's wishes. We return to this point in question 6 when we consider important principles for designing a new regulatory framework for GE/GM organisms.

3.4   As agricultural policy is a devolved area of legislation, Defra should consider and consult early and in depth with the devolved administrations.

Public acceptability

3.5   Experience from the introduction of GMOs in the 1990s indicates that changes to food products made without the informed agreement of consumers are likely to be met with resistance and rejection, even when scientists and regulators are satisfied with their safety. Clarity and transparency about how products are created and approved will be needed to gain trust.

3.6   Public support is essential to realising the benefits of genome editing. Setting out clear goals for agricultural policy as described above, would help to ensure, and allow the public to be assured, that introduction of a novel variety or breed is consistent with the outcomes that people want from UK agriculture.

3.7   A broad public dialogue is necessary prior to any attempts to bring new products to the market, and throughout the process of development to market, if the decision to do so is made. As part of this, it will be necessary to set out the choices we face and provide a chance for people to have their say. This will entail describing the benefits of developing crops that do not require pesticides, or can grow in future climates, as well as the consequences for the planet and the human population of failing to develop these. Trade-offs will need to be highlighted, alongside the opportunity cost involved in focus of our resource on development of one set of potential management solutions over others.

3.8   A smart, coordinated engagement plan, developed with a broad cross-section of experts (including social scientists), would be advisable to present the science about genome edited products. The public may reasonably wish to know what benefits will be obtained through the use of genome edited products before being expected to accept them, and an engagement plan could help to convey this.

3.9   There are a number of reasons why genome edited products might engender consumer opposition, besides safety concerns. These may include:

   a. Public attitudes to the use of animals, both in research[39] and in the food supply chain (e.g. veganism). We discussed this in more detail in our response to the Nuffield Council on Bioethics[40] (see point 2.8 and 3.3, particularly).

   b. Association between technological innovation and intensive farming. For example, some may consider genome editing a 'techno-fix' to tackle the symptoms of industrial farming rather than an approach that can be locally-adapted to provide alternative farming practices. In fact, application of genome editing could develop crops requiring reduced chemical and fertiliser use, hence less intensive farming.

   c. Government must be careful not to overhype the technology itself and avoid making unsubstantiated promises. There is the need to carefully consider the language used and promote educational approaches, which focus on the message that "genome editing is only a genetic improvement method, or rather a set of methods – nothing more, nothing less", albeit with great potential to improve current practices in agricultural breeding and beyond[41]. The use of jargon is unhelpful. Rather than using the traditional method of stating the 'pros and cons' of using genome editing,

[39] IPSOS MORI (2018). Attitudes to animal research in 2018.
[40] Royal Society of Biology, 2019. Royal Society of Biology response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals'
[41] Blancke, S. et al. (2017). De-Problematizing 'GMOs'. Suggestions for Communicating about Genetic Engineering.

conversations with the public should discuss potential 'trade-offs' of genome editing and other approaches to meet sustainable goals.

d. Patent rights and the control of food by multinational companies. The issue of patents is addressed further below. Reducing the barriers of current GMO regulation that makes registration impossible for all but the biggest corporations could, in fact, enable more competition and reduce the dominance of a few large companies in agricultural biotechnology (see also answer to Question 6).

e. Perception that a regulatory change is aligned with a particular political position. This could relate to how market access or consumer choice is supported, and how this is framed.

Labelling

3.10   Some people will not wish to consume genome edited products for reasons that may be deeply personal and associated with strongly held values. It is important that the development of new regulations considers the impacts on these people. An important question is whether genome edited produce should be labelled as such. Our members expressed divided views.

3.11   On one hand, labelling of genome edited products facilitates consumer choice and provides transparency. On the other hand, labels are not required for products bred using other processes such as radiation mutagenesis, and labels could convey that the product carries a risk where none exists, putting consumers off and potentially generating pressure for supermarkets to refuse to stock them. Where changes could have been produced by traditional breeding, testing and enforcement of labels may not be possible.

3.12   Mandatory labelling is not justified on scientific grounds, as genome edited products are not associated with greater risks than traditionally bred equivalents, and on balance it would be preferable were mandatory labels restricted only to known health issues such as the presence of allergens or nutritional composition. However, breeders could be required to disclose the use of genome editing to allow for transparency. Should the market demand it and consumers be willing to pay for it, products free from genome editing could be segregated and labelled to serve these consumers.

Effects of agriculture on climate, biodiversity, wellbeing and animal welfare

3.13   Agriculture is a major contributor to climate change and biodiversity loss. It now faces a situation in which it must 'do more with less'; providing nutritionally high quality food for a growing global population while reducing its use of land, water and energy; all in the context of a changing climate that makes food production by current methods more difficult.

3.14   Animal and plant breeding, alongside other approaches, are a means to address this situation, and accelerated research is needed to improve the efficiency of food production and supply, and reduce waste, globally. While it still takes many years to produce new varieties, breeding with genome editing proceeds more quickly than traditional methods. With a rapidly closing window to prevent the most drastic effects of climate change, and an urgent

need to halt and reverse biodiversity loss, all approaches should be considered to bring about the necessary improvements in food production. This includes considering the use of modern breeding methods, such genome editing, where it is carried out for purposes beneficial to society.

3.15   In the UK, the NFU has set out its goal for agriculture to become carbon neutral by 2040. This ambitious target will require many approaches to reducing resource use, increasing efficiency and storing carbon. Genome editing can help to achieve this target, for instance with crops more resistant to diseases, so that energy-intensive agricultural inputs go further with less produce wasted, and more land can be spared for carbon storage and nature.

3.16   The precision enabled by genome editing, in comparison with traditional breeding, increases the speed and efficiency with which beneficial improvements can be brought into use. In animal breeding this could have positive animal welfare consequences. On one hand, GE can improve rapidity and efficiency in breeding programmes by avoiding generations of selection within breed, or the need for backcrossing to regain genetic merit after introgression of genes derived from inferior breeds[42]. If use of GE resulted in a reduction of animals used in breeding programmes or more refined ways to obtain an equal level of genetic gain relative to current practices, then the decision to refuse to use the technology would be ethically questionable[43]. Additionally, GE could be used to correct genetic defects that arose spontaneously through traditional animal breeding with the main objective of improving the animals' quality of life, such as the correction of isoleucyl-tRNA synthetase (IARS) syndrome in Japanese black cattle using CRISPR[44]. Importantly, a similar outcome, namely the creation of *de novo* favourable alleles[45], would be almost impossible to achieve via traditional breeding.

3.17   In our response to the Nuffield Council on Bioethics call for evidence on 'genome editing in farmed animals' we highlighted some of the technical constraints, namely our understanding of genome-phenome relationships and the type of assisted reproduction techniques (ARTs) deployed, which should be considered in applying GE technologies to livestock species. However, since then, advances have been made to improve on the limitations. Different ARTs present different limitations both in terms of their applicability to a given species but also in their impact on the progeny. Particularly in the case of ruminants, the use of ARTs (e.g. in vitro embryo culture or nuclear transfer) is often associated with major developmental problems, including large offspring syndrome[46]. However, advances in early zygotic or oocytes microinjections reduce bovine embryo mosaicism rates replacing the need for somatic cell nuclear transfer and therefore reducing the likelihood of large calf syndrome[47].

[42] Eriksson, E., et al. (2018). Breeding and ethical perspectives on genetically modified and genome edited cattle.
[43] Royal Society of Biology, 2019. Royal Society of Biology response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals' . Please see point 3.2.
[44] Ikeda, M et al (2017). Correction of a disease mutation using CRISPR/Cas9-assisted genome editing in Japanese Black cattle.
[45] Tait-Burkard, C. et al. (2018). Op.cit (see footnote 35).
[46] Hill, J.R. (2014). Incidence of abnormal offspring from cloning and other assisted reproductive technologies.
[47] Lamas-Toranzo, I. et al. (2019). Strategies to reduce genetic mosaicism following CRISPR-mediated genome edition in bovine embryos.

Improved editing pipelines in mammalian embryos using electroporation increases the efficiency of the techniques both in bovine and porcine zygotes[48] and recently-developed methods for genome editing of chickens also show high efficiency[49]. Animal welfare assessment to be conducted in a GE project can be complicated by our limited understanding of the full spectrum of what different genes do. Genes can often have different roles in different tissues and are subject to complex tissue-specific regulatory mechanisms[50]. Additional research and technological advances will shed light on the underlying biological complexity, therefore a future regulatory system should be agile and proportionate in managing risks for animal welfare, should potential hazards be identified.

3.18 Genome editing could improve human health and wellbeing through development of products with enhanced nutritional profiles. As one example, the development of crops that synthesise omega-3 "fish oils" has potentially large implications for both human health and the conservation of endangered fish stocks, as well as enormous economic potential.[51,52]

3.19 Genome editing can be used to create crop varieties that are safer for consumers, such as wheat with reduced free asparagine content that reduces levels of the probable carcinogen acrylamide accumulated during cooking. Decisions about a future regulatory regime should consider the risks of maintaining the current regulations that are extremely inhibitory to the development of genome edited organisms. These include the risks to consumers from food that could be made safer using genome editing, as well as the environmental and economic risks of continuing on current unsustainable trajectories. The latter are grave and apparent, and all the available tools should be considered to protect our ecosystems while providing healthy, safe food, environments, and grown commodities.

Implications for trade and investment

3.20 Enabling UK farmers to grow genome edited products could help them to compete with those in other parts of the world where these methods are already used commercially. However, it may equally exclude markets, depending on the regulatory requirements of the trading partner country in question. The rules around exporting genome edited products and any risk to trade, particularly with the EU, will need to be thoroughly assessed and communicated. The European Commission is currently reviewing the status of novel genomic techniques under Union Law, the outcome of which will be relevant to this issue.[53] Incorporation in plant variety registration of a genome edited status notification would provide transparency to support trade.

3.21 Providing a route to market for products created by genome editing could unlock overseas investment by major breeding companies, attracted by the strength of the UK science base.

[48] Miao, D. et al (2019). Simplified pipelines for genetic engineering of mammalian embryos by CRISPR-Cas9 electroporation.

[49] Ballantyne, J. et al. (2021). Direct allele introgression into pure chicken breeds using Sire Dam Surrogate (SDS) mating.

[50] Royal Society of Biology, 2019. Royal Society of Biology response to the Nuffield Council on Bioethics call for evidence on 'Genome Editing and Farmed Animals'. See point 1.4

[51] Rothamsted Research, 2018. Where GM meets GE

[52] Rothamsted Research, 2019. GM Camelina Trial: Frequently Asked Questions.

[53] John Innes Centre, 2021. A CRISPR picture emerges on European Union GMO directive.

It could also draw people into working in the biosciences. However, the size of the UK market is relatively small. Depending on the cost of meeting regulatory requirements, investor companies might calculate that products developed specifically for the UK would not recoup the financial cost of breeding, and therefore prefer products that can be sold in the EU as well as the UK. Currently, some UK research into genome edited crops has led to technological advances which are being exported to other countries for commercial application, with the UK losing out on capitalising commercially on our research and development capabilities.

Reduced need for animal testing

3.22   Risk assessments of GM food and feed introduced by the EU require 90-day feeding trials in laboratory rodents.[54] By focussing on safety assessment based on appropriate, science-based test guidelines, new regulation for genome editing could avoid unnecessary use of experimental animals. A thorough review of the available data, such as the seventh Framework Programme for Research (FP7) data and other relevant datasets, as foreseen in the Regulation (EC) No 503/2003, could inform strategies for replacement of animal testing. Where individual proteins expressed in an organism require testing, an OECD toxicity test can be used.

Intellectual property

3.23   Breeders and research institutions must pay for licences to use the tools for genome editing in the creation of commercial products. Genome editing work done in the UK today cannot be used for commercial products, unless the laboratories have already taken licenses, which many may be yet to do.

3.24   Having lost out to the US in generating the primary IP associated with genome editing, the UK risks becoming very far behind if it fails to become active in generating future innovations in the technology.

3.25   In plant breeding, products from traditional breeding are protected by Plant Breeders' Rights (PBR), which are granted to the breeder of a new variety as well as any patent that may be awarded. PBR gives the breeder exclusive control over the propagating material for a certain number of years. However, there is tension over the relationship between PBR and patent rights, which, in many cases are considered to be overlapping and not mutually exclusive.

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[54] European Commission, 2013. Commission implementing regulation (EU) no 503/2013.

4.

What criteria should be used to determine whether an organism produced by gene editing or another genetic technology, could have been produced by traditional breeding or not?

Please provide evidence to support your response.

4.1 No clear criteria can be described that would determine whether an organism produced by genome editing or other genetic technologies could have been produced by traditional breeding. This means no clarity can be achieved using this principle, and it is not appropriate as the basis of regulation. A workable basis for regulation, adaptable to future methodological developments, would be based on assessing characteristics of the products of breeding, as described in the response to question 1 and subsequent questions.

4.2 Traditional breeding includes methods by which it is possible to move genes between closely related crop species. Further, processes involved in natural selection, and in traditional breeding, can produce a wide range of mutations, ranging from single base substitutions, insertions and deletions through to larger changes such as inversions of chromosome sectors and duplications. Genes may be silenced, activated or modified by epigenetic processes. The genome of the sweet potato contains two stretches of DNA from bacteria, which are expressed in various tissues, and is an example of a naturally occurring GMO.[55,56] This is just one of many hundreds of examples of 'horizontal gene transfer', in which genetic material is acquired by plants, animals, or microbes from a different organism via natural, biological processes (other than transmission from parent to offspring).[57,58]

4.3 Genetic changes such as these can produce useful and beneficial improvements in the organisms on which we depend for sustenance, and without such mutation events occurring, we would not have the domesticated varieties that produce food for humans. Frequent – and sometimes large – genetic changes occur regularly in breeding using traditional methods, and the use of genome editing would be no different, nor have any differing effect on the safety of an organism so produced. Further, the size of a genetic change is not necessarily related to the magnitude of its effect on the product.

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[55] Kyndt, T. et al. (2015). The genome of cultivated sweet potato contains Agrobacterium T-DNAs with expressed genes: An example of a naturally transgenic food crop.

[56] Nature, 2015. Sweet potato is already a GM crop.

[57] Emamalipour et al., 2020. Horizontal Gene Transfer: From Evolutionary Flexibility to Disease

[58] For example, a study in 2015 concluded that the human genome has acquired 145 foreign genes during its evolution (see: Crisp et al (2015). Expression of multiple horizontally acquired genes is a hallmark of both vertebrate and invertebrate genomes.)

Part 2: QUESTIONS ON BROAD REFORM OF LEGISLATION GOVERNING ORGANISMS PRODUCED USING GENETIC TECHNOLOGIES

This part of the consultation is designed to start the process of evidence gathering to inform how Defra should reform its approach to regulating novel organisms in the longer term. There are two questions that focus on areas where views and evidence would be welcome.

These questions do not apply to the use of genetic technologies in contained use conditions (e.g. in laboratories) or to the use of genetic technologies in humans (e.g. gene editing of human embryos).

5.

There are a number of existing, non-GM regulations that control the use of organisms and/or products derived from them. The GMO legislation applies additional controls when the organism or product has been developed using particular technologies.

Do you think existing, non-GM legislation is sufficient to deal with all organisms irrespective of the way that they were produced or is additional legislation needed? Please indicate whether, yes, the existing non-GMO legislation is sufficient, or no, existing non-GMO legislation is insufficient and additional governance measures (regulatory or non-regulatory) are needed.

5.1 There is broad consensus in our membership that certain products developed using genetic technologies need a streamlined regulatory approval process within scope of existing non-GMO legislation and we discussed some of the relevant criteria for exempting products from GM risk assessment in answers to earlier questions.

5.2 It is important that a streamlined process captures any residual uncertainties associated with product development (if any are expected), and that it is adaptive to sector-specific applications, and responsive to any technological developments. This can be achieved within the remit of current legislation with a rational, science-based and proportional use of risk assessment and through expert advice to the relevant regulatory authorities.

5.3 This adaptation must safeguard public confidence in the regulatory system, which of course must remain trustworthy to engender such confidence. There is a risk that the perception of a major overhaul of the inherited UK legislation at this stage could cause a public reaction and the erosion of citizen's trust, which is a potential outcome that must be avoided. Citizens must be active participants in a dialogue towards a reform of genetic technologies regulations. However, pressure or interest must not steer the regulatory reform away from an evidence-based approach that supports sustainable and responsible innovation for the benefit of people and the environment.

Short term adaptations of the current regulatory system:

5.4 In the short term, the main focus should be to amend the legislation so that certain GE products will no longer be regulated under the GMO legislation (particularly in those cases where there is straightforward substantial equivalence[59] or familiarity[60] with traditionally bred comparators). In cases where GE organisms are exempted, the existing non-GMO legislation will be sufficient to ensure that products of GE will not cause harm to human or animal health or the environment.

5.5 Again in the short term, GE products that are determined to be GMOs, or other GMOs, can be assessed under the transposed EU legislation. In doing so it should be noted that such legislation has not been implemented pragmatically in the EU which has resulted in lengthy delays to the approval process and disproportionate data requests.[61,62] A lot of time and resources have been devoted by EFSA expert panels in developing guidance documents (34 between 2006 and 2019). Despite the fact that EFSA opinions are mostly evidence-based, these documents specify in increasing detail "not only what data developers must compile for their applications, but how these data need to be generated and analysed. This is an obvious deviation from the regulatory frameworks set by countries that support agricultural biotechnology, which use the expertise and experience of their risk assessors to judge what data may be relevant for the safety assessments and the quality of the data submitted".[63]

5.6 It has been suggested that appeals to scientific uncertainty used to justify an unduly onerous risk assessment may in fact be a means to delay cultivation of a GM crop under political pressure.[64] At the level of the EU Council of Ministers some member states will always vote against any use of GMOs (including the use of products of genome editing) whereas others will vote for, leading to delays or blockage. The lack of separation of science-based risk assessment from other aspects of political decision-making has been flagged as a major drawback of the experience at the EU level.[65] The UK Government should reflect on how to safeguard both a science-based risk assessment and a transparent and inclusive political decision-making process, while communicating the different and independent processes and outcomes to citizens clearly.

5.7 As suggested in point 1.11, at first the UK can use and adapt the legislation it has inherited, ensuring that legal timelines are adhered to and EFSA guidelines are applied in a scientific manner using Article 5 of the Regulation EC No 503/2003 which allows for a derogation to be applied in cases where studies are not scientifically justified.[66] DEFRA should also consider using Article 7 of the transposed

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[59] Kuiper HA, et al. (2002). Substantial equivalence—an appropriate paradigm for the safety assessment of genetically modified foods?

[60] "Concepts of familiarity and substantial equivalence remain important to establishing a comparative baseline for the risk/safety assessment process. And the stated intent of risk/safety analysis for GEOs/GMOs remains a stepwise, case-by-case paradigm in concept" in Wolt, J. (2019). Op. cit. (see footnote 38).

[61] EuropaBio, (2011). Approvals of GMO in the European Union.

[62] Garcia-Alonso, M. and Holt, K. (2020). Fostering innovation in agriculture through enabling regulatory policy. Page 25 – The EU regulatory environment.

[63] Garcia-Alonso, M. and Holt, K. (2020). Op.cit. (see footnote 63)

[64] Raybould, A. and Poppy, G.M. (2011). Commercializing genetically modified crops under EU regulations - Objectives and barriers.

[65] For example see https://www.feednavigator.com/Article/2016/01/19/EU-Ombudsman-reprimands-Commission-over-GM-food-and-feed-approval-delays

[66] "Article 5 - Scientific requirements for the risk assessment of genetically modified food and feed for applications submitted under Articles 5(3) and 17(3). Point 2. By way of derogation from paragraph 1, an application may be submitted that does not satisfy all the requirements of that paragraph provided that: (a) particular information is not necessary owing to the nature of the genetic modification or of the product; or (b) it is not scientifically necessary, or technically possible to supply such information. The applicant shall submit reasoned justification for the derogation." Regulation EC No 503/2003

EU GMO Directive 2001/18/EC,[67] which allows for "differentiated procedures", whenever the conditions are met. This means that certain GMOs or other products of gene technology, for example, products of genome editing, can be subject to simplified procedures. The UK could use this inherited article in the near term to address categories of products, developed using GE, that do not present additional hazards with respect to traditionally bred counterparts (e.g. organisms that have no foreign DNA sequence insertion).

5.8   Case-by-case decisions could evolve towards authorizations at a different level of grouping or categorisation in the future, as experience of approval accumulates. The introduction of categories of products 'generally recognised as safe'[68] has been suggested and should be considered, particularly as part of the development of a new regulatory framework focused on products and traits (e.g. known agricultural traits, such as a leaner animal, versus novel traits, like producing a non-host product).

General considerations on the risk assessment of GE/GM organisms

5.9   There is no such thing as zero risk and the potential of an unrecognised hazard is always there, hence the importance of hazard identification in conventional risk assessment, which must be evidence-based.[69] The OECD, FAO and WHO foundational work on safety and risk assessment stressed that "risk/safety analysis comprises hazard identification and, if a hazard has been identified, then risk assessment".[70] This is something very different from how the European risk assessment regime for GE/GM organisms has operated in practice so far. Risk assessment became "a pro forma activity regardless of case-specific attributes of the product and its intended use",[71] which is widely considered unjustified. The UK must reform its approach to risk assessment of GE/GM organisms.

5.10   Acceptability of risk is normally decided by comparison with a defined baseline, which leads to a comparative paradigm for risk analysis. This paradigm proceeds from the concept of familiarity or 'substantial equivalence' (OECD 1993),[72] which recognizes that "knowledge and experience with a commonly bred organism, its environment, the trait and their interactions guides the need for a risk assessment".[73] Establishing substantial equivalence serves as "a starting point from which to structure a program to demonstrate any potential differences from the comparator which, if detected, can be evaluated in terms of safety" (WHO 2000),[74] but does not amount to a safety assessment in itself. The comparative approach is well accepted at the global level both in the Codex Alimentarius (CA)[75] and at the OECD,[76] of which the UK is a participant. The comparative approach is used mainly in food/feed safety assessment. A new product is compared with an existing counterpart, which has a

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[67] "Article 7 - Differentiated procedures. Point 1. If sufficient experience has been obtained of releases of certain GMOs in certain ecosystems and the GMOs concerned meet the criteria set out in Annex V, a competent authority may submit to the Commission a reasoned proposal for the application of differentiated procedures to such types of GMOs." EU Directive 2001/18/EC

[68] Generally Recognized As Safe or "GRAS" is a regulatory concept developed by the U.S. Food and Drug Administration

[69] Wolt, J. (2019). Op. cit. (see footnote 38).

[70] OECD (Organization for Economic Cooperation and Development) (1993). Safety evaluation of foods derived by modern biotechnology: concepts and principles.

[71] Wolt, J. (2019). Op. cit. (see footnote 38).

[72] OECD (Organization for Economic Cooperation and Development) (1993) Safety evaluation of foods derived by modern biotechnology: concepts and principles.

[73] Wolt, J. (2019). Op. cit. (see footnote 38).

[74] WHO (World Health Organization) (2000) Safety aspects of genetically modified foods of plant origin: report of a joint FAO/WHO Expert Consultation. World Health Organization, Geneva

[75] Codex Alimentarius (2009) Foods Derived from Modern Biotechnology (2nd Ed.). Codex Alimentarius Commission, Joint FAO/WHO Food Standards Program. http://www.fao.org/3/a157a1554e.pdf

[76] OECD (2019) Introduction to OECD work on novel food and feed safety. In Safety 159 Assessment of Foods and Feeds Derived from Transgenic Crops, Volume 3, Common Bean, Kearns et al., Biotechnology and biosafety policy at OECD: Future trends (manuscript)

history of safe use, on the basis of key components such as nutrients, anti-nutrients, toxins and allergens. In line with the CA Commission, OECD has published over 40 consensus documents on the quantitative key components of those specific crops used in genetic modification against which a comparison can be made.[77] This approach is important because it should inform targeted evaluations of novel food irrespective of the technique used to produce them,[78] steering away from the blanket requirement to conduct tests only for GM/GE organisms simply because they use recombinant DNA and genome editing technologies in the production phase – a goal for the future regulatory system. The concept of familiarity with traditionally bred crops has some merit. Livestock breeding has also a long history of using genetic diversity for animal improvement and the breeds developed accordingly to existing breeding programmes could provide a useful baseline and comparator for GE/GM animals.[79]

5.11 As mentioned in our answer to question 4, these sorts of comparisons between traditionally bred and GE/GM organisms might not always be straightforward. Novelty (lack of substantial equivalence or history of safe use) of a trait or product could act as a regulatory trigger and guide regulators in determining the need and scope for additional risk/safety assessment in a stepwise, case-by-case manner. For example, genome editing of host factors (e.g. cellular receptors) to make livestock animals resistant to a zoonotic disease may require a carefully thought-through regulatory approval pathway from proof of concept stage to commercial release, via progressive stages of biocontainment, intermediate small scale releases and longer term monitoring/surveillance of emerging impacts. For example, scientists are studying species-specific susceptibility factors to influenza A viruses,[80] some of which are adapted to humans and have pandemic potential. Genome editing could offer ways to introduce resistance to avian-specific viruses in farmed chicken to alleviate the poultry sector of an enormous health and welfare challenge. However, GE targeted host factors could be conserved between birds and humans therefore introducing the risk of driving the evolution of influenza towards a form that is more likely to infect humans and other mammals. This is not a new problem and is analogous to the rise of antimicrobial resistance due to uncontrolled use of antimicrobials in people and farmed animals. Tackling avian influenza in poultry can benefit the animals and also reduce the risk of the emergence of human-adapted viruses if the use of genetics and other practices is appropriately managed and balanced.

5.12 With respect to the environment, risks from the release of GE/GM organisms could be: "1) direct but unanticipated effects of modified organisms on non-target species; (2) effects on the outcome of direct interactions among species; (3) alteration of indirect relationships between species; (4) influences on the biochemical processes that support all ecosystems; and (5) changes in the rate and direction of the evolutionary responses of species to each other and to their physical and chemical

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[77] http://www.oecd.org/env/ehs/biotrack/consensusdocumentsfortheworkonharmonisationofregulatoryoversightinbiotechnologybiologyofcrops.htm

[78] The two major food hazards are whether the food is poisonous and whether it is allergenic. The baseline recognises that all human foods and animal feeds are poisonous if too much is ingested, so it is taken as the normal dose of the food or feed, i.e. substantial equivalence which is analogous to the familiarity concept. The assessment asks the question: is the normal dose of modified food or feed significantly more toxic to the human or animal populations than the unmodified food or feed? The presence of a toxin may arise from the introduced gene or indirectly from the modification process. In cases where food has significant natural toxins (e.g. lectins in beans, cyanogenic glycosides in cassava) the modification may be directed at reducing the natural toxin. Allergenicity affects only a certain proportion of the population. The potential allergenicity of the product of a new event can be determined by a range of tests. The safety of non-GM and GM food and feed is determined by the UK Food Standard Agency which has updated the EU-related aspects to account for Brexit.

[79] UK Government (8 March 2021). Guide to zootechnical rules and standards – Breeding programmes.

[80] Long, JS., et al. (2019). Species specific differences in use of ANP32 proteins by influenza A virus.

environments".[81] The baseline for the assessment, which is generally accepted, is the environmental impact of the non-manipulated organism grown in that region. In this context too, it is the potential impact of the specific trait introduced or features of the organism that would inform decisions about risk assessment. For example, in crop breeding, major hazards are: (a) changes in agricultural practice to take advantage of the trait, e.g. leading to large areas of monoculture resulting in adverse consequences such as loss of biodiversity and possibly greater impact on climate change. Alternatively, use of herbicide-tolerant crops can facilitate low or no tillage weed control, with the beneficial outcomes of a reduction in soil erosion and water runoff, to be balanced with the negative effects of herbicide use on biodiversity and in driving resistance. (b) Gene flow to sexually compatible species. Pollen from herbicide-tolerant crops could fertilize sexually compatible wild species resulting in them becoming resistant to herbicide and thus increasing weed problems. Similarly, pollen from insect-resistant crops can spread to sexually compatible species in the environment making them lethal to targeted insects; alternatively, the use of insect-resistant crops reduces the need for insecticide applications and the subsequent loss of non-targeted insect species. Field trials will provide early evidence of the complexity of outcomes and suggest balanced approaches to more extensive release of the organisms and longer term monitoring of impacts, if required.

5.13 A review of GMO risk assessment and approval processes should take into account numerous references indicating the safety of currently commercialised GMOs[82] and the results of different research programmes which looked for adverse effects (see for example the FP7 data described above and the Commission research programme).[83] These data suggest that the commercial GMOs to date do not pose greater risks than their conventional counterparts. In the case of crops, it also suggests that the process of genetic modification has not produced unintended adverse effects within the plant. Other regulators, such as Argentina, Japan and the USDA have reviewed their legislation and have adapted and modified their legislation to take into account the history of safe use of GMOs since they were introduced over 25 years ago.

5.14 Finally, as discussed in answer to question 6, it is important to frame product approval questions related to safety within wider consideration of policy objectives, expected benefits and protection goals.

Integration of regulatory assessment and approval of GE organisms within existing regulations

5.15 The safety of exempted GE organisms for human consumption and environmental impacts will be properly assessed under existing legislation (e.g. the Food Safety Act, Environmental Protection Act and Plant Variety Regulations) and by relevant competent authorities (e.g. the Food Standards Agency, with input from the Advisory Committee on Novel Foods and Processes; the Environment Agency, with input from Advisory Committee on Releases to the Environment, and the Health and Safety Executive, with input from the Scientific Advisory Committee on Genetic Modification).

5.16 Post marketing monitoring for exempted products should follow equivalent rules to those applied to products obtained with other methods (e.g. traditional or organic).

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[81] OECD (Organization for Economic Cooperation and Development) (1986). Recombinant DNA safety considerations.

[82] Food Navigator (2021). Japan GM food safety update: Transgenic soy, rapeseed have no impact on biodiversity even after 15 years – government study

[83] European Commission (2010). A decade of EU-funded GMO research.

5.17   Given the breadth of applications and the potential of genetic technologies, the safety assessment and quality assurance of products must be carried out by multiple government agencies in a concerted manner (akin to what happens in the U.S. where multiple agencies are led by the U.S. Department of Agriculture and the Food and Drug Administration).

5.18   We believe the UK government can achieve this goal effectively but, in the process of approving GE products to market or releasing them in the environment, there will be the need to strengthen cross-department cooperation, accountability and government interaction with other sectors of society.

5.19   Citizens must be supported and trusted to appreciate how robust the existing regulatory processes are. In reaching out to them with the right set of information campaigns and citizen involvement projects, Government can gain trust back,[84] becoming a trustworthy guardian of public and environmental safety. The Food Standards Agency has already a track record for similar initiatives (see the project 'Trust in a changing world'),[85] which should be built on.

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[84] Society Inside and Fraunhofer (2020). Trust and tech governance.
[85] Food Standards Agency (2018). Trust in a changing world

6.

Where you have answered no (existing, non-GMO legislation is insufficient to deal with organisms produced by genetic technologies), please describe what additional regulatory or non-regulatory measures you think are required to address this insufficiency, including any changes you think need to be made to existing non-GMO legislation. Please explain how any additional measures you identify should be triggered (for example: novelty, risk, other factors).

Please provide evidence to support your response.

6.1   We welcome DEFRA's evidence gathering with the objective to reform the regulation of novel organisms developed using modern biotechnologies. The UK has an opportunity to develop a new regulatory framework fit for the 21st century, and has a history of leadership in the development of regulations and guidelines in the field of biotechnology, which includes successes like: the development of the Human Fertilisation and Embryology Act and the establishment of the Human Fertilisation and Embryology Authority (HFEA).

6.2   A new regulatory system for novel organisms should support disruptive innovation and facilitate global knowledge transfer and trade, through a process that is sustainable and responsible.

6.3   Here and in answer to question 5, we propose a pragmatic and phased approach from the current framework towards a new regulatory system that focuses on expected benefits and policy objectives, builds on previous foundational work and can effectively integrate within existing regulations. We list a number of principles that should be considered when designing this new framework.

A pragmatic, phased and enabling approach to regulatory reform

6.4   In our answer to question 5, we described adaptations of the current UK regulatory system that the Government can enact in the short term. These adaptations will bring the UK in line with other countries that support innovation in this field, such as Japan, Australia and Argentina, which have adopted a more nuanced approach to products of genome editing while Argentina also has a long history of commercial use of GMOs.

6.5   The new regulatory framework must realise the full potential of genome editing while at the same time upholding the high standards of human safety, animal welfare and environmental protection, to which the UK is committed. A more permissive regulatory environment should not come at the expense of citizens' confidence in the decision-making and safety assessment processes, which will need to be accessible, transparent and communicated appropriately.

6.6   The case of Argentina also provides evidence of how a more permissive regulatory system can enable disruptive innovation. The developers of GMOs in Argentina are large foreign multinationals whereas developers of GE organisms tend to be smaller enterprises with a

broader range of products[86]. The UK already lists a number of innovative small and medium enterprises (SMEs) and public research institutions that could develop GE products for locally-adapted and sustainable agricultural projects, both in the UK and in low and middle income countries. Unleashing their potential would also support the growth of the country's bioeconomy.

6.7   In the medium to long term, the UK should perform a review of the legislation and determine whether or not it is fit for purpose. Overall, a transition towards a product and trait focused regulatory system is welcomed by the research sector[87].

Design principles for a new regulatory framework

A focus on expected benefits, policy objectives and protection goals:

6.8   Having clear policy and protection goals will ensure the relevant risk assessment questions are asked and thus enable a thorough assessment of potential risks, such as those that were identified in relation to farmland diversity and discussed earlier in this document, as well as understanding the benefits.

6.9   Expected benefits of approving GE/GM organisms, as well as the impacts of missed opportunities, should be considered in order to achieve a balance between benefits and risks (see point 6.30 about precautionary approaches).

6.10   A set of societal opportunities and policy objectives for the use of genetic technologies were identified by members of the Society in 2019:

    i.   making plant and animal breeding more accurate, efficient and better adapted to local needs of human populations and environments;

    ii.   improving animal health and welfare;

    iii.   improving food security and tackling malnutrition;

    iv.   improving food safety;

    v.   improving sustainability (e.g. through more efficient use of land and other resources);

    vi.   limiting climate change and environmental degradation;

    vii.   protecting and preserving biodiversity and ecosystems;

    viii. support innovation and support the uptake of existing and novel technologies in a sustainable and responsible manner.

6.11   Clear protection goals linked to policy objectives should not be technology/product specific but applied to entire production sectors, for example agriculture, and be compatible with sustainable development goals. This will ensure that food production is maintained

[86] Whelan, A., et al. (2020). Gene Editing Regulation and Innovation Economics.
[87] UK Research and Innovation – Biotechnology and Biological Sciences Research Council (2015). Position statement on new crop breeding tools.

sustainably while meeting national and international biodiversity and environmental protection targets. Where necessary, stewardship guidelines can accompany product introduction to ensure human and animal health and the environment are protected.

The importance of global alignment

6.12 Scientists and innovators call for regulatory alignment and common standards at a global level. Trade rules and the benefits/impacts of innovation act both on a global and local scale, therefore a governance system should integrate both levels effectively.

6.13 Ideally, the global aspect of this governance system should be adopted by all nations to identify potential risks to food and feed and to the environment, and to satisfy international agreements and regulations. Global frameworks and initiatives to consider are: United Nations Framework Convention on Climate Change, SDGs, WHO, WTO, Convention on Biodiversity (including the Nagoya Protocol on Access and Benefits Sharing), Cartagena Protocol, and other initiatives tackling major problems (e.g. AMR).

6.14 Furthermore, because of international commitments, it is unlikely that the UK can dispense from certain concepts used in GMO regulation, which are internationally agreed and enshrined in global treaties and protocols (e.g. Cartagena, Codex Alimentarius) and should therefore be considered in the development of a new regulatory system for the UK.

6.15 The local part of the governance system should advise decision makers on local or regional problems (e.g. food insecurity but also varying cultural, social and ethical aspects) and enable the decision makers to balance benefit against loss of opportunities (e.g. food security for their population against loss of trade).

6.16 Global alignment would also support ongoing internationally-led programmes (e.g. under the auspices of the FAO) in low and middle income countries where small and medium enterprises (SMEs) and on-the-ground initiatives are trying to use genetic technologies in locally-adapted research programmes and applications.

Scope of the new regulatory system and integration with existing legislation

6.17 The terms Genetic Manipulation and GMO carry unfortunate "baggage" as being the main focus of campaign opposition to the technology and raise public mistrust[88]. Some of our members would welcome a more encompassing and coherent regulatory system that covers traditional breeding, transgenic technology (formerly GM), genome editing, and other bioengineering technologies, as the boundaries between these methods and their applications are blurring[89]. A rational, coherent and integrated legislative framework would encompass different sectors and organisms by linking up national, local food and environmental regulations.

6.18 Given commitments under the Codex Alimentarius, CPB and other international treaties, Government will be need to subject certain GE/GM products to progressive levels of

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[88] Hull, R. et al., (2021). See chapter 9. Op. cit (see footnote 11)

[89] Wieczorek, A.M. and Wright, M.G. (2012). History of agricultural biotechnology: how crop development has evolved.

additional regulatory oversight. However, in the future, it should be possible to rely predominantly on non-GM legislation for general human, animal and environmental safety, and supplement this legislation with additional requirements as necessary, as previously described.

Responsible research and innovation in product development and application of biotechnologies

6.19 Principles of responsible research and innovation should be included in the development of a new governance framework[90]. Ethical questions will arise along the R&D pipeline: from conception of a project and early stage research to product development, regulatory approval and release, with subsequent impacts on people and the environment.

6.20 We discussed ethical issues in the context of farmed animals in a recent submission to the Nuffield Council on Bioethics consultation on 'genome editing and farmed animals'[91]. There will be other relevant questions to ask from a governance standpoint, such as: participatory ways to include citizen's views and aspirations; questions of fairness of access and inclusivity in decision-making processes; ethical standards of research conduct, which are culturally appropriate and avoid exploitation of resources. As part of this, it is important to make sure that genome editing, and genetic technologies in general, are not perceived as solely a 'Western' technology, or utilized as such. Equally, as in any context, UK GE regulatory change should not bring negative externalities for other nations, through indirect large-scale change to their agricultural practices via market forces, leading to damaging effects on food security or loss of biodiversity, for example.

6.21 Transparency of the regulatory process should engender citizens' trust[92]. Third sector scientific organisations, like the national academies and learned societies, can collaborate with the Government to enable a dialogue on the use of genetic technologies and support the development of efficient, effective and accessible routes of knowledge exchange.

Regulatory triggers

6.22 The main regulatory trigger should be the potential impact that a product has on human food and health, animal health and welfare, the environment and agricultural practices, in the context of policy objectives and protection goals (see 6.8-6.11). Consideration of novelty (e.g. nature of the change/trait or presence of 'foreign' DNA) and potential hazards (e.g. biosafety considerations[93] or potential for non-target effects) will be incorporated in the risk assessment (see answer to question 5). All new varieties/events should be considered as products rather than processes and on a case-by-case basis.

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[90] Agapito-Tenfen, et al., (2018). Revisiting risk governance of GM plants: the need to consider new and emerging gene-editing techniques.
[91] See footnote 9
[92] Society Inside and Fraunhofer (2020). Trust and tech governance.
[93] Hull, R. et al., (2021). Op. cit (see footnote 11)

Proportional and smart regulations

6.23   Proportional and smart regulation should encourage research to tackle increasing constraints on agricultural production, in the context of societal need and global challenges, and with due consideration for the efficiency and effectiveness of obtaining regulatory release permissions.

6.24   There are common features associated with national regulatory systems more enabling to innovation, such as[94]:

   a.   Guidelines that are not overly prescriptive [see paragraphs 5.6 and 5.7].

   b.   Risk assessments conducted by dedicated, highly trained risk assessors enabled to apply expert judgement and a proportional approach to the risk assessments.

   c.   Provision for extensive consultation with applicants both during product development and throughout the assessment period providing advice on what data they may need for the assessment.

   d.   Flexibility in the data requirements depending on the nature of the product [see answer to question 5].

6.25   This shift could encourage SMEs to be set up in resource-poor countries to tackle situations such as local food production problems in orphan crops (especially in centres of origin) which are potentially of no interest to large multinational companies.

A flexible and adaptive system

6.26   Regulation should be flexible and adapt rapidly to market, agronomic and policy conditions (e.g. climate change raising new constraints to crop production, changing demographics leading to food insecurity), which may shift policy objectives and require fast responses.

6.27   A regulatory system should be able to deal rapidly and consistently with new and emerging technologies and new uses of products (e.g. plant-based and insect meat substitutes, plants engineered to produce cosmetics and pharmaceuticals).

6.28   Regulatory requirements should be regularly reviewed to incorporate the growing body of evidence (e.g. safety of use). After decades of successful introduction of GM crops the USDA performed a review of the legislation and adopted a more streamlined approach for GE and GM products known as the SECURE legislation.

Precautionary approaches

6.29   The new regulatory system should include the Precautionary Approach[95]. If the Precautionary Principle is favoured instead, regulators need to pay attention to its interpretation and implementation in order to avoid the imposition of disproportionate regulations without

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[94] Garcia-Alonso, M. and Holt, K. (2020). Op.cit. (see footnote 63)

[95] "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. (Principle 15), Rio Declaration on Environment and Development, 1992.

conclusive evidence of harm[96]. In all cases, the potential benefits and costs of action or lack of action must be considered alongside appropriate precautionary measures[97].

6.30 Novel traits, which have not been previously risk assessed or do not have a history of safe use and which could only be produced by genetic modification, may require additional scrutiny. However, a search for unintended effects using comparative approaches should not be disproportionate to any possible perceived risk. The requirement for additional risk assessment should be science and evidence based and focus on possible adverse effects of the trait.

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[96] Hull, R. et al., (2021). See pages 119-122. Op. cit (see footnote 11)

[97] The Society of Biology (2014). GM foods and application of the precautionary principle in Europe.

Appendix 1

Summary of current global regulation challenges

The EU harmonised emerging national regulations on the laboratory use of recombinant DNA (rDNA) regulations in 1982 and 1984 (Council Recommendation 82/472/EC; Council of Europe Recommendation R(84)16).

The first GM plants were produced in 1983 (antibiotic- resistant tobacco) and the first field release (virus-resistant tobacco in China) was in 1992. The EU produced two directives for GMOs in 1990, Directive 90/219/EEC for contained use and Directive 90/220/EEC for deliberate release to the environment; these were subsequently revised by Directive 98/81/EC for contained use and Directive 2001/18/EC for release.

At the international level, the Organisation for Economic Cooperation and Development (OECD) issued a document "Recombinant DNA Safety Considerations" in 1986 and its follow-up "Safety Considerations for Biotechnology" in 1992; these documents influenced the development and evolution of national biosafety regulations. However, regulators have often failed to adhere to the spirit of a stepwise, case-by-case approach to design and develop safety assessment of GM organisms, as initially postulated in foundational work by the OECD, FAO and WHO. This shortcoming translated to statutory requirements that result in "studies, costs and timelines that are inconsistent with the lack of identifiable harms (hazards) associated with rDNA technology"[98] and risk assessment is but "a pro forma activity regardless of case-specific attributes of the product and its intended use"[99].

Also in 1992 The Rio Convention on Biological Diversity (CBD) contained two articles relevant to biotechnology (see article 8(g) and article 19) which led to the Cartagena Protocol (2000) regulating transboundary movement between nations of GMOs (termed Living Modified Organisms) – particularly, see articles 1 (protection goals and sustainability), 15 (science-based risk assessment), 23 (public involvement in decision making), article 26 (socioeconomic considerations) and annex III (principles for scientific risk assessment).

GMO biosafety issues are also covered by the World Trade Organisation and the Codex Alimentarius.

National regulatory structures can be grouped into two categories depending on the regulatory trigger, which is the GMO event that prompts regulatory oversight.

- Product-based regulations. These assume that there is no scientific basis to treat GMOs differently to the products of traditional breeding and thus, regulatory scrutiny is proportional. It requires comparison with traditionally bred products that have similar or identical phenotype. The choice of comparators can be difficult, leading to problems in establishing familiarity and/or substantial equivalence.
- Processed-based regulations. These assume that GM technology itself represents a new set of risks. The advantages are that traceability is facilitated and post-commercialization can be monitored (e.g. through labelling). The disadvantages are that the system is slow

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[98] Wolt, J. (2019). Op. cit. (see footnote 38).
[99] Wolt, J. (2019). Op. cit. (see footnote 38).

and expensive especially in proportion to risk, products developed from traditional breeding could be potentially risky but escape regulatory scrutiny and amendments of regulations may be required to allow alignment with scientific progress.

Other countries, i.e. Canada, have product-based regulations and controls Plants with Novel Traits (PNTs) be they produced from traditional breeding or by genetic manipulation. It was however suggested that current application of the Plants with Novel Traits (PNT) regulations represents a barrier to potential innovation and investment within the plant breeding sector in terms of applying gene editing technologies, particularly in public sector research[100].

Other regulatory authorities, e.g. the EU, have process-based regulations with Directive 2001/18/EC defining "*genetically-modified organism (GMO) means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*". Many countries, e.g. USA, have a combination of the two regulatory triggers, which can cause difficulties in trading and impede the implementation of the Cartagena Protocol (which in fact the US has not ratified).

Thus, many of the regulations on release of GMOs, be they of crops, animals or other organisms are becoming out-of-date and confusing internationally as based on conflicting concepts (e.g. product v process); furthermore, most are not able to keep up with rapidly changing situations - e.g. climate change, demographic changes, new technologies.

There have been several proposals for reforming the current regulations mostly suggesting amendments to the EU regulations, some general[101,102] and some especially in light of the European Court of Justice judgement on GE products[103,104] ; others are amendments to existing regulations to cover GE technology [e.g. in Australia, Overview of Gene Technology Amendment (2019 Measures No. 1) Regulations 2001] and specifically for developing countries[105].

These amendments are patches on existing regulations due to development of new techniques and applications and do not always deal with the improved characteristics of GE and GM products, which could help tackling global challenges.

[100] Smyth, S.J., et al. (2020). Regulatory Barriers to Innovative Plant Breeding in Canada.

[101] Davison, J. and Ammann, K. (2017). New GMO regulations for old: determining a new future for EU crop biotechnology.

[102] Bratlie, S. et al. (2019). A novel governance framework for GMO.

[103] Wasmer, M. (2019). Roads forward for European GMO policy – uncertainties in wake of ECJ judgement have to be mitigated by regulatory reform.

[104] Eriksson, D., et al. (2020). Options to Reform the European Union Legislation on GMOs: Scope and Definitions.

[105] Adenle, A.A. et al. (2018). Rationalizing governance of genetically modified products in developing countries.

Appendix 2: Member Organisations of the Royal Society of Biology

Full Organisational Members

Agriculture and Horticulture Development Board
Anatomical Society
Association for the Study of Animal Behaviour
Association of Applied Biologists
Association of Reproductive and Clinical Scientists (ARCS)
Bat Conservation Trust
Biochemical Society
British Association for Lung Research
British Association for Psychopharmacology
British Biophysical Society
British Ecological Society
British Lichen Society
British Microcirculation and Vascular Biology Society
British Mycological Society
British Neuroscience Association
British Pharmacological Society
British Phycological Society
British Society for Cell Biology
British Society for Developmental Biology
British Society for Gene and Cell Therapy
British Society for Immunology
British Society for Matrix Biology
British Society for Neuroendocrinology
British Society for Parasitology
British Society for Plant Pathology
British Society for Proteome Research
British Society for Research on Ageing
British Society of Animal Science
British Society of Plant Breeders
British Society of Soil Science
British Society of Toxicological Pathology
British Toxicology Society
Daphne Jackson Trust
Fisheries Society of the British Isles
Fondazione Guido Bernardini
GARNet
Gatsby Plant Science Education Programme
Genetics Society
Heads of University Centres of Biomedical Science
Institute of Animal Technology
Laboratory Animal Science Association
Linnean Society of London
Microbiology Society

MONOGRAM – Cereal and Grasses Research Community
Network of Researchers on the Chemical Evolution of Life
Nutrition Society
Quekett Microscopical Club
Society for Applied Microbiology
Society for Experimental Biology
Society for Reproduction and Fertility
Society for the Study of Human Biology
South London Botanical Institute
The Field Studies Council
The Physiological Society
The Rosaceae Network
Tropical Agriculture Association
UK Brassica Research Community
UK Environmental Mutagen Society
University Bioscience Managers' Association
Zoological Society of London

Supporting Organisational Members

Animal & Plant Health Agency (APHA)
Association of the British Pharmaceutical Industry (ABPI)
AstraZeneca
BioIndustry Association
Biotechnology and Biological Sciences Research Council (BBSRC)
British Science Association
Covance
Ethical Medicines Industry Group
Fera
Institute of Physics
Ipsen
Medical Research Council (MRC)
NNedPro Global Centre for Nutrition and Health
Northern Ireland Water
Porton Biopharma
Royal Society for Public Health
Severn Trent Water
Syngenta
Understanding Animal Research
Unilever UK Ltd
United Kingdom Science Park Association
Wellcome Trust
Wessex Water
Wiley Blackwell

Collated published responses from the Royal Society of Biology to previous consultations and inquiries can be found in our online and searchable Policy Resource Library:
https://my.rsb.org.uk/item.php?orgresourceid=1