Response to DEFRA Consultation on "The Regulation of Genetic Technologies"

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Section 1 - About you

1. Would you like your response to remain confidential?

b. No

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Response

We thank Defra for the opportunity to respond to this consultation. Colleagues from SPRU and IDS have been actively researching UK and international management and regulation of biotechnology for over forty years. Much of our work in recent years has been conducted through the ESRC STEPS Centre and is available at the Centre's biotechnology research archive. With regard to question 7, most of this research has focussed on the cultivation of crop plants, human food and animal feed, although we study the social, economic and institutional factors that are relevant to these and other sectors/activities.

Before addressing the questions in Sections 2 and 3, we would like to express our concern that the way this consultation is framed, through the CitizenSpace questionnaire, does not allow for a robust scientific engagement with the issues. Not only does it force institutions to adopt monolithic positions by requiring singular responses in "an official capacity as a representative of an academic institution," but the format of the multi-choice questions 10, 11, 12 and 14, oversimplifies the issues at stake, and leaves no room for plural and conditional advisory responses (Stirling 2010) exploring considerations associated with a number of options, which we judge to be most appropriate in this context. We believe that this undermines the legitimacy of the consultation, and we are concerned that it contributes to polarising the debate at an early stage. Here we respond to the questions (as numbered in the online consultation questionnaire) using open text responses to explore the scientific and policy issues more fully than the questionnaire allows. Before doing so, we raise some further general issues regarding the consultation.

The fact that this consultation is taking place at a time when most of the country is in lockdown due to the Coronavirus makes it very difficult for some groups to engage (drawing into question principle G of the 2018 Consultation Principles)[1]. While the Coronavirus itself has little scientific salience in the current consultation, the social response to the pandemic is shaping the context in which this consultation, and subsequent government decisions, are emerging. The need for careful democratic deliberation on the basis of scientific evidence is heightened by the fact that the Coronavirus has unfortunately already precipitated conspiracy theories (Freeman et al 2020) that, combined with government actions (Fancourt et al 2020) and lack of transparency (Commons Science and Technology Committee 2021), may have a negative effect on trust in the science-politics interface. In this atmosphere of mistrust and misinformation about the relationship between scientific expertise and politics in decision-making, it will be more difficult to advance the stated objectives of this policy process. Trust urgently needs to be rebuilt if any future policies on genetic technologies (and other approaches) are to combine with other developments (e.g. the Agriculture Act and Environmental Land Management Scheme) to improve agricultural productivity and food security in a way that enhances the natural environment.

This consultation has been framed very narrowly, and it conspicuously fails to address numerous important issues. While the consultation document tells us what the government does not want to do (regulate GEOs like GMOs, in accordance with judgement of the European Court of Justice in case C-528/16 - Confédération paysanne and Others), it does not tell us

[1] Principle G. Consultations should take account of the groups being consulted. Consult stakeholders in a way that suits them. Charities may need more time to respond than businesses, for example. When the consultation spans all or part of a holiday period, consider how this may affect consultation and take appropriate mitigating action, such as prior discussion with key interested parties or extension of the consultation deadline beyond the holiday period.

what it does want to do. We are told that the government is considering dealing with GEOs in ways that are different from those that apply to GMOs, but few clues are given as to what might be the characteristics of that alternative regime, except for implying that it could be less demanding for applicants than that for GMOs. It is not even clear if the government wants to require some form of scientific risk assessment of GEOs, or whether it envisages exempting GEOs (or some subset of that category) from any such requirement. It is not clear if the government wants to require the presence of GEOs to be labelled, or whether it envisages exempting GEOs (or some subset thereof) from that requirement. Consequently when responding to the consultation, we are in large measure commenting on proposals that are remarkably vague.

Those problems are compounded by a set of serious inadequacies in the prevailing regulatory regime for GMOs, although such shortcomings are not confined to that category of technologies. Firstly, the types of risk assessments to which GMOs have been subjected have been manifestly inadequate in scope. They focus too narrowly on only a few putative risks, and those risks are assumed always to be entirely independent of each other, between which no synergies can occur. Risk assessments rely on modest amounts of data from only a few studies conducted in only a few situations, which are then assumed to be suitably representative of all possible circumstances (Hilbeck et al 2020). Secondly, official risk assessment methodologies have been framed by organisations and individuals closely linked to those with powerful interests in the commercialisation of those technologies and products. Thirdly, risk managers often frame their policy goals by reference to those with powerful interests in the commercialisation of those technologies and products rather than a focus on the protection of public and environmental health; notwithstanding rhetorical claims to the contrary. Fourthly, the practical consequences of the prevailing policy regime is that it externalises adverse consequences of unforeseen and unaddressed risks onto the most vulnerable communities and environments.

The costs of remediating any unforeseen and unaddressed adverse effects can dwarf any estimated benefits that the prevailing regimes might claim to provide. The example of the BSE (or Mad Cow Disease) saga demonstrated that an initial investment of some £20 million pounds in the mid-1980s, to eradicate BSE infected material from the UK's herds and feed chain, would have avoided the UK government subsequently incurring costs of some £20 billions in the aftermath of the admission in March 1996 that meat from infected cattle was causing cases on new-variant-CJD (van Zwanenberg & Millstone, 2005). If the precautionary investment of £20 millions in 1985-6 had been made, however, evidence of the consequent savings would never have emerged. The payoff from precautionary measures may often not be directly identifiable, but that, in itself, is not a good reason for choosing not to take precautions. Similar findings with other novel technologies or practices, including antimicrobials as growth promoters, PCBs (EEA 2001), pesticides such as DDT, DBCP and imidacloprid, and invasive species (EEA 2013). While these may seem unrelated to the current consultation, we argue that they are vitally important for the government to consider as part of its approach. In particular, the uncertainties associated with GE point to the need for broader democratic engagement to inform decision-making.

Finally, whilst this consultation relates to England, we find it difficult to imagine the implications of further regulatory divergence between the devolved administrations around such a fundamental issue. Therefore we have assumed the continued integrity of the UK's internal market and responded on the basis of the decisions facing the UK.

Section 2 - Part 1: The regulation of GMOs which could have been developed using traditional breeding methods

This part of this 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.

10. 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 a GMO

Not applicable; it is not possible to provide a scientifically robust response by answering either "yes" or "no."

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

See our responses to questions 11, 12 and 13 below. We encourage the government to take into account the uncertainties that we highlight in its decisions over how to regulate gene edited crops and/or livestock and look beyond this binary framing. Alternative regulatory approaches involving international co-ordination and techniques such as whole genome sequencing (WGS), Polymerase Chain Reaction (PCR) or other 'omics- based tools associated with identification, labelling, monitoring and insurance requirements would have significant implications for the UK and our international partners.

11. 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?
- Similar
- Lesser
- Greater

Not applicable; it is not possible to provide a scientifically robust response by answering either "similar", "lesser" or "greater". Possible harms from all possible GE products cannot be accurately characterised with a single adjective, unless it is 'unknown' or 'indeterminate', given that we do not know which GEOs might be developed.

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).

See our response to question 13.

The category “GE or other genetic technologies” is not sufficiently well-defined to enable this question to be robustly answered. Whilst for some forms of GE “their traditionally bred counterparts” can be understood as genetically identical organisms resulting from traditional breeding, for “other genetic technologies” it is not clear what this refers to (especially if this category is to apply to all possible future genetic technologies).

Beyond the lack of clarity about the categories proposed for comparison, there are multiple other considerations that follow directly and/or indirectly as a result of gene editing that affect the “risk of harm to human health or the environment”. Taking the first application/ area (cultivation of crop plants) as an example, there are various combinations of crop plants, traits, agricultural practices and ecological and socio-economic contexts that have a bearing on risk and uncertainty. Whilst individual instances of gene editing may not, on their own, affect the “risk of harm to human health or the environment”, the potential for rapid and widespread use of gene editing in the UK and internationally increases uncertainties and limits our ability to foresee or to manage risks, should they appear.

In examining these uncertainties, we first address the question at the level of specific approaches to gene editing. At the genetic level, unintended effects have been documented and discussed in the following studies and reviews, among others (see Table 1). Taken together, these studies illustrate that site-directed nucleases and associated gene editing systems in plants, including ZFN, TALENs and CRISPR/Cas-9, raise the possibility of unintended off-target changes (elsewhere in the genome to the target site), unpredictable on-target changes, non-Mendelian inheritance patterns, including in rice, barley and other cereals, *Brassica oleracea* and soybean. Whole genome sequencing and other approaches (Zischewski et al 2017, Kawall et al 2020) can can help to clarify unintended effects, and reviews (Modrzejewski et al 2020) have contributed to an increased understanding of the underlying factors that can cause them. Nevertheless, uncertainties remain and, even with careful design, elimination of unintended effects cannot be guaranteed. Furthermore the widespread use of these sequencing approaches raises significant “non-safety” issues (see 12).

Beyond the direct implications for plants, other studies also indicate wider uncertainties associated with incomplete understandings of the mechanisms by which gene editing can cause unintended changes (Zischewski et al 2017, Shin et al 2017, Eckerstorfer et al 2019, Ledford 2020, Kawall et al 2020). Experiments in animals, humans and cell studies raise additional questions, for example about the limitations of current approaches in fully characterising SDN-related changes (Anderson et al 2018, Skryabin BV et al. 2020).

Table 1. Selection of peer-reviewed publications demonstrating unintended effects from gene editing in plants, animals and humans

Unintended effects in Plants	● Biswas, Sukumar & Tian, Jiaqi & Rong, Li & Chen, Xiaofei & Luo, Zhijing & Chen, Mingjiao & Zhao, Xiangxiang & Zhang, Dabing & Persson, Staffan & Yuan, Zheng & Shi, Jianxin. (2020) Investigation of CRISPR/Cas9-induced SD1 rice mutants highlights the importance of molecular characterization in plant molecular breeding. *Journal of Genetics and Genomics*. 47. https://doi.org/10.1016/j.jgg.2020.04.004 ● Ishizaki, T. (2016) CRISPR/Cas9 in rice can induce new mutations in later generations, leading to chimerism and unpredicted segregation of the targeted mutation. *Molecular Breeding* 36, 165. ● Jin S, Zong Y, Gao Q, Zhu Z, Wang Y, Qin P, Liang C, Wang D, Qiu JL, Zhang F, Gao C (2019) Cytosine, but not adenine, base editors induce genome-wide off-target mutations in rice. *Science* 364(6437):292–295. https://doi.org/10.1126/science.aaw7166 ● Lawrenson T, Shorinola O, Stacey N, Li C, Ostergaard L, Patron N, Uauy C, Harwood W (2015) Induction of targeted, heritable mutations in barley and *Brassica oleracea* using RNA-guided Cas9 nuclease. *Genome Biology* 16:258. https://doi.org/10.1186/s13059-015-0826-7 ● Modrzejewski D, Hartung F, Sprink T, Krause D, Kohl C, Wilhelm R (2019) What is the available evidence for the range of applications of genome-editing as a new tool for plant trait modification and the potential occurrence of associated off-target effects: a systematic map. *Environmental Evidence* 8:27. https://doi.org/10.1186/s13750-019-0171-5 ● Wolt JD, Wang K, Sashital D, Lawrence-Dill CJ (2016) Achieving plant CRISPR targeting that limits off-target effects. *Plant Genome* 9(3):1–8. https://doi.org/10.3835/plantgenome2016.05.0047 ● Xu, R. F., Li, H., Qin, R. Y., Li, J., Qiu, C. H., Yang, Y. C., Ma, H., Li, L., Wei, P. C., & Yang, J. B. (2015). Generation of inheritable and "transgene clean" targeted genome-modified rice in later generations using the CRISPR/Cas9 system. *Scientific reports*, 5, 11491. https://doi.org/10.1038/srep11491 ● Zhao H., Wolt J.D. (2017), Risk associated with off-target plant genome editing and methods for its limitation. *Emerging Topics in Life Sciences* 1 (2): 231–240. doi: https://doi.org/10.1042/ETLS20170037 ● Zhu C, Bortesi L, Baysal C, Twyman RM, Fischer R, Capell T, Schillberg S, Christou P (2017) Characteristics of genome editing mutations in cereal crops. *Trends in Plant Science* 22(1):38–52. https://doi.org/10.1016/j.tplants.2016.08.009 ● Zischewski, J., Fischer, R., and Bortesi, L. (2017). Detection of on-target and off-target mutations generated by CRISPR/Cas9 and other sequence-specific nucleases. *Biotechnology Advances* 35, 95–104. https://doi.org/10.1016/j.biotechadv.2016.12.003

Unintended effects in Animals	● Anderson, K. R., Haeussler, M., Watanabe, C., Janakiraman, V., Lund, J., Modrusan, Z., et al. (2018). CRISPR off-target analysis in genetically engineered rats and mice. *Nature Methods* 15, 512–514. doi: 10.1038/s41592-018-0011-5 ● Farris, M.H., Texter, P.A., Mora, A.A. et al. Detection of CRISPR-mediated genome modifications through altered methylation patterns of CpG islands. *BMC Genomics* 21, 856 (2020). https://doi.org/10.1186/s12864-020-07233-2 ● Guo, R., Wan, Y., Xu, D. et al. (2016) Generation and evaluation of Myostatin knock-out rabbits and goats using CRISPR/Cas9 system. *Scientific Reports* 6, 29855. https://doi.org/10.1038/srep29855 ● Kosicki M, Tomberg K, Bradley A (2018) Repair of double-strand breaks induced by CRISPR-Cas9 leads to large deletions and complex rearrangements. *Nature Biotechnology* 36(8):765–771. https://doi.org/10.1038/nbt.4192 ● Norris, A.L., Lee, S.S., Greenlees, K.J. et al. Template plasmid integration in germline genome-edited cattle. *Nature Biotechnology* 38, 163–164 (2020). https://doi.org/10.1038/s41587-019-0394-6 ● Qian, L., Tang, M., Yang, J. et al. (2015) Targeted mutations in myostatin by zinc-finger nucleases result in double-muscled phenotype in Meishan pigs. *Scientific Reports* 5, 14435. https://doi.org/10.1038/srep14435 ● Ryu J, Prather RS, Lee K (2018) Use of gene-editing technology to introduce targeted modifications in pigs. *Journal of Animal Sciences and Biotechnology* 9:5. https://doi.org/10.1186/s40104-017-0228-7 ● Shin HY, Wang C, Lee HK, Yoo KH, Zeng X, Kuhns T, Yang CM, Mohr T, Liu C, Hennighausen L (2017) CRISPR/Cas9 targeting events cause complex deletions and insertions at 17 sites in the mouse genome. *Nature Communications* 8:15464. https://doi.org/10.1038/ncomms15464 ● Skryabin BV et al. (2020). Pervasive head-to-tail insertions of DNA templates mask desired CRISPR-Cas9–mediated genome editing events. *Science Advances* 12 Feb 2020: Vol. 6, no. 7, eaax2941. DOI: 10.1126/sciadv.aax2941. ● Wang, G., Du, M., Wang, J., & Zhu, T. F. (2018). Genetic variation may confound analysis of CRISPR-Cas9 off-target mutations. *Cell Discovery*, 4, 18. https://doi.org/10.1038/s41421-018-0025-2 ● Zuo E, Sun Y, Wei W, Yuan T, Ying W, Sun H, Yuan L, Steinmetz LM, Li Y, Yang H (2019) Cytosine base editor generates substantial off-target single-nucleotide variants in mouse embryos. *Science* 364(6437):289–292. https://doi.org/10.1126/science.aav9973
Unintended effects in Humans / Cell studies	● Grunewald J, Zhou R, Garcia SP, Iyer S, Lareau CA, Aryee MJ, Joung JK (2019) Transcriptome-wide off-target RNA editing induced by CRISPR-guided DNA base editors. *Nature* 569(7756):433–437. https://doi.org/10.1038/s41586-019-1161-z ● Kapahnke M, Banning A, Tikkanen R (2016) Random splicing of several exons caused by a single base change in the target exon of CRISPR/Cas9 mediated gene knockout. *Cells* 5(4):45. https://doi.org/10.3390/cells5040045 ● Lalonde, S., Stone, O. A., Lessard, S., Lavertu, A., Desjardins, J., Beaudoin, M., Rivas, M., Stainier, D., & Lettre, G. (2017). Frameshift indels introduced by genome editing can lead to in-frame exon skipping. *PLOS One*, 12(6), e0178700. https://doi.org/10.1371/journal.pone.0178700 ● Mou, H., Smith, J.L., Peng, L. et al. (2017) CRISPR/Cas9-mediated genome editing induces exon skipping by alternative splicing or exon deletion. *Genome Biology* 18, 108. https://doi.org/10.1186/s13059-017-1237-8 ● Murugan K, Seetharam AS, Severin AJ, Sashital DG. (2020) CRISPR-Cas12a has widespread off-target and dsDNA-nicking effects. *Journal of Biological Chemistry* 295(17):5538-5553. doi: 10.1074/jbc.RA120.012933

	● Sharpe, J.J., Cooper, T.A. (2017) Unexpected consequences: exon skipping caused by CRISPR-generated mutations. *Genome Biology* 18, 109. https://doi.org/10.1186/s13059-017-1240-0 ● Tuladhar, R., Yeu, Y., Tyler Piazza, J. et al. (2019) CRISPR-Cas9-based mutagenesis frequently provokes on-target mRNA misregulation. *Nature Communications* 10, 4056. https://doi.org/10.1038/s41467-019-12028-5 ● Smits, A. H., Ziebell, F., Joberty, G., Zinn, N., Mueller, W. F., Clauder-Münster, S., Eberhard, D., Fälth Savitski, M., Grandi, P., Jakob, P., Michon, A. M., Sun, H., Tessmer, K., Bürckstümmer, T., Bantscheff, M., Steinmetz, L. M., Drewes, G., & Huber, W. (2019). Biological plasticity rescues target activity in CRISPR knock outs. *Nature methods*, 16(11), 1087–1093. https://doi.org/10.1038/s41592-019-0614-5

Whilst the studies listed in Table 1 show that uncertainties prevail at the genetic level, wider uncertainties characterise the consequences of subsequent gene interactions within the organism, and with its receiving bio-physical, behavioural and socio-economic environments (discussed to some extent elsewhere by Troadec et al 2019).

Various studies illustrate how the bio-physical and socio-economic environments (contrasting agro-ecologies or socio-ecological niches) impact on the performance of particular crops or technologies, and thus their suitability in different contexts (Ojiem et al 2006, Nyagumbo et al 2016, Descheemaeker et al 2019). It has long been argued that such considerations are also relevant in the assessment of environmental risks from GMOs (Millstone and Van Zwanenberg 2003). The relevance of behavioural environments was illustrated by the farm scale evaluations (Hawes et al 2003), which demonstrated indirect effects on biodiversity as a result of specific management regimes adopted alongside herbicide tolerant GM crops. Experiences of insect resistance management associated with Bt crops also illustrate the importance of socio-economic conditions and the scale and type of farming that is predominant in different contexts. These kinds of findings have diverse implications in each of the applications/ areas. Further uncertainties emerge as a result of the “non-safety” issues discussed in 12 below.

12. 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

Yes, depending on how they were regulated.

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

See our response to question 13.

All of these issues are relevant, and whilst they are described as “non-safety” issues, they do have potential implications for human health and the environment. We add another category: liability and insurance.

Trade:

Trade implications apply to both UK exports and imports, and depending on other countries’ regulatory decisions, could disrupt the international food trade and the UK’s food security.

UK agri-food and drink exports reached nearly £24 billion prior to the pandemic, with France and Ireland amongst the top export partners and Australia and New Zealand seen as potential growth markets post-Brexit (FDF 2021). If the UK were to permit GE crop cultivation, this would affect UK exports to jurisdictions that did not permit foods containing these GE ingredients. UK exports to countries in the EU, as well as New Zealand and Australia, which currently require labelling of certain gene edited foods, would be jeopardised in the absence of traceability mechanisms that were able to demonstrate their GE-free characteristics (or other characteristics, depending on the importing countries’ laws).

Current decisions over the regulation of genetic technologies also raise implications for UK imports. Article 2.3 of the World Trade Organisation Sanitary and Phytosanitary Agreement (SPS), to which the UK is a signatory, prohibits countries from arbitrarily or unjustifiably regulating the safety of foods differently on the basis of whether they are produced domestically or come from overseas. To fulfil our obligations under this agreement, the UK would need to regulate gene edited imports on the same basis as those produced in the UK. Therefore any requirements for WGS-based (or alternative) characterisation or PCR-based (or alternative) labelling, monitoring or insurance would need to be applied consistently. The fact that gene editing is being undertaken more frequently and in more parts of the world requires that decisions taken domestically address this international context.

The decisions taken by the UK which affect the regulation of GE products could also have implications for producers in developing countries that export agricultural commodities to the UK, especially if they also export to other countries, which regulate GE products in a different way. The specific effects will depend on the type of commodity and the nature of the trading relationship, for example, whether it is practically and economically feasible to segregate production and supply chains of GE and non-GE products or products intended for domestic vs. export markets, or to draw distinctions between food, feed and other products. Nearly 20 years ago, the “GM Nation?” public debate recognised that developing countries have special interests. These should be taken into account in government decision-making.

Strict approaches to labelling and monitoring imports and exports to and from the UK may be possible in theory (see our answer to question 13). However, it would be financially and practically impossible to implement an international food trade system that screens all imports and exports using current WGS or PCR methods, let alone more sophisticated techniques. Such a course of action would likely obstruct the international trade in food products, with significant negative implications for the UK and other countries. Impacts on developing countries with lower regulatory capacity might be even more severe, especially in instances where new evidence led to the withdrawal of products that were difficult to identify and trace.

Consumer choice:

Regardless of food safety considerations, a significant proportion of UK consumers wish to be able to identify whether or not their food is GM or GE. Recent studies show a narrow majority thought GM food (defined as “plants which have had their genes altered”) should not be allowed (Curtice et al 2021) and find overall support for continuing high food standards and food labelling post-Brexit (Curtice et al 2021), including among “red wall” voters (Cracknell & Rose, 2021). This raises significant challenges. Our answer to 13 regarding traceability is pertinent to this issue.

Under Retained EU law, the presence of any genetically modified ingredients has to be declared on the label, unless the GM component accounts for less than 0.9% of that ingredient. In whichever way the products of GE might be officially portrayed, it is likely that consumers will view gene editing as a form of ‘genetic modification’. If the UK’s food labelling regulations were changed so that the products of gene editing were exempted from the GM labelling provisions the public would rightly feel deprived, and perhaps also cheated, of information to which they had previously been entitled. That would seriously undermine public confidence in the safety and acceptability of the UK’s food supply.

Labelling is also an indispensable requirement for transparency and traceability of ingredients through the food chain. Traceability is not just something that is nice to have, and helpful for consumers, it is a legal requirement for those who sell food products (see for example FSA 2019).

All Food Business Operators are strictly responsible for the safety of the food which they produce, distribute or sell. They must not place on the market any food if it is injurious to health or unfit for human consumption. They must also comply with food law in the production, distribution, storage and sale of food, which includes being able to trace suppliers of their food and the business customers that they have supplied. They must be able to remove unsafe food from the market in the event of a food safety incident. All of those obligations are dependent on proper labelling of food products and the ingredients of which they are composed. The 2013 ‘Horsemeat saga’ demonstrated, amongst other things, the importance of truthful labelling and full traceability.

Consequently labelling of products that contain GEOs will be essential to enable food businesses to trade lawfully; it is a requirement for consumer confidence, and it is also indispensable for e.g. Trading Standards Officers, Environmental Health Officers and Public Analysts to discharge their statutory duties.

Intellectual property:

It is not clear how the proposed regulatory changes would affect intellectual property protection in relation to gene edited organisms (GEOs), however our answer to question 13 regarding traceability is pertinent to the enforcement of such IP. Intellectual property protection under retained EU law (Directive 98/44 on the protection of biotechnological inventions) could be subject to diverse interpretations in the UK and EU nations, and divergence with other trading partners (e.g. the USA) is also likely.

It is perhaps also worth noting on this point - as was observed in a previous UK Government Chief Scientist's Annual Report (Government Office for Science 2014) - that it is commercial interests around intellectual property rights that form a major driver of the disproportionate attention and investment that is allocated to genetic (including gene editing) innovations. This comes at the expense of more systemic, but neglected, social innovations around ecological agriculture, open source seed production, and participatory farmer collaboration platforms. If the Government wishes to be as effective as possible across different fields, it should not just be focusing on *'what can gene editing do for this challenge?'.* Instead it should ask: *'which among many diverse innovation trajectories can be most effective in responding to this challenge?'* Agro-ecological approaches are widely ignored in established business models, despite their evident promise (UN FAO, 2019).

Animal welfare:

Given the broad potential for gene editing applications, the resulting changes to agriculture that these could precipitate/ allow, and our limited understanding of subjective animal experience, the UK's policy choices have significant implications for animal welfare.

Liability and insurance:

Given the applicability of 'strict liability' provisions of retained EU law, it would be prudent to require producers of gene-edited crops (or those produced by other genetic technologies) to obtain insurance cover against their potential liabilities for adverse effects on human health and/or the environment. This would couple effectively with a requirement for GE products to be labelled and traceable – see our answer to question 13.

Like other aspects of any potential future regulatory framework, this requirement would have differential implications for firms of different sizes, with some potentially more readily able to access such insurance than others. It would also have unequal impacts across countries, given the different availability of insurance across national contexts.

Further, it is important to be clear here, that neither insurance nor liability instruments have the effect of reducing incertitude. Instead they simply help to transfer responsibilities, impacts and blame. By defining harm, limiting damage and channelling responsibility (for instance), liability rules make it possible for insurance to be obtained by food business operators and developers. By quantifying and distributing the burden of addressing any impacts thereby recognised, (re)insurance arrangements tend to be more important for the support they give industry, than the protection they afford others. Intractable uncertainties, ambiguities and ignorance not addressed by any given insurance-liability framework remain extant, but can become less visible. The adverse consequences of any surprises tend to fall on nature, the state and/or the most vulnerable people, rather (in a 'polluter pays' manner) on those interests promulgating the innovations in question.

13. 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.

This is a complex question, which is central to the assumptions underpinning the consultation.

As explained in our answer to question 11, unintended effects occur with various forms of gene editing that – while they do not all entail known risks – do create uncertainties, not all of which are tractable. As residual uncertainties are inevitable, initial regulatory appraisals will need to be complemented with post-market monitoring, which will also require labelling and traceability. This will also require methods to detect GE products in the food chain. The criteria to determine "products that could have been produced by traditional breeding or not" therefore need to be both scientifically and legally robust under national and international law. This may not be possible, however here we discuss some options.

Our answers to questions 10, 11, and 12 assume that establishing the criteria referred to in question 13 is achievable. However, we set out below various considerations and questions that require answers (possibly supported by further research) in order to establish whether this is the case. Throughout, we use the distinction between SDN-1, SDN-2 and SDN-3, as proposed by EFSA (EFSA GMO Panel 2012; 2020) and Sprink et al (2016, Fig. 2).

First it is worth considering what types of changes can emerge from "traditional breeding." "Traditional breeding" is not defined in the consultation document. We assume that it includes selective breeding with and without the use of chemical or radiation mutagenesis. Products of these types of breeding currently require no environmental or human safety assessment under UK law. However, they can result in diverse changes from single base pairs (equivalent to SDN-1) to multi-site changes (equivalent to multiplex SDN-1), longer translocations or chromosomal rearrangements (equivalent to some forms of SDN-2 or SDN-3). They can also result in unintended effects of the kinds discussed in 11 (Anderson et al 2016), raising the potential for adverse effects on food safety and environmental impact. Given current knowledge of the range of outcomes that have been achieved through traditional breeding, all intra-species modifications could conceivably be included in this vague category.

To date, most of our experience with gene editing involves individual, small changes. However, considering technological developments, the government should also take into account the potential for multiplexed, simultaneous or successive rounds of gene editing (rather than individual edits to a "wild type" genome, prior to editing) offered by new gene editing techniques (Kawall 2019). An example would be case study 2, as studied by the EFSA GMO Panel (2021), which would involve edits in numerous target genes. Crossing or further editing of such an example would lead to evermore complex alterations in comparison to any "wild type" against which a new GE product might be compared, even though it in theory "could have been produced by traditional breeding".

Option 1: Full characterisation of the whole genome and subsequent labelling and traceability

Whether or not all unintended changes will be detectable or identifiable at the level of individual GE organisms is an unresolved question and depends upon the techniques applied (Modrejewski et al 2020). Mandatory guidelines specifying the characterisation of GE

organisms would provide consistent data. Whole genome sequencing (WGS) may provide an option for characterising specific gene edited organisms at the moment when they are produced. However, traceability is more challenging. Even when testing foods in their non-processed forms, the available approaches to detection of GE products are imperfect and costly, especially if taken to scale. For GE organisms that had been characterised, WGS could thereafter be used to provide information about the presence of genetically identical products, although at significant expense. PCR-based detection is often used in the detection and identification of GMOs, by detecting the presence of particular transgenes (see below) and could be applied in the case of GEOs. Chhalliyil et al (2020), for example, provide a mechanism for using PCR to identify a particular GE *Brassica* product, although this does not in itself distinguish whether it was produced via gene editing or traditional breeding. PCR would be easier to apply to SDN-2 and SDN-3 products than SDN-1.

The ability to identify GE products through PCR requires the development of PCR tests based on clear knowledge of the sequences present in that product. As such, in order to apply this approach in international trade we suggest a mandatory international registry of biotech products be established (see Eckersdorfer et al 2018) that can act as a reference against which to develop testing tools. Existing initiatives fall far short of the type of intergovernmental co-ordination that would be required in order to provide adequate, authoritative and comprehensive information.

The government should give very serious consideration to encouraging a mandatory international registry of biotech (including gene edited) products, and the provision that UK trade should be confined to countries that sign up to implementing such a registry. It is worth noting that some countries that export to the UK (e.g. the USA) already appear to have moved to a situation in which some gene edited products can now be commercialised without any regulatory oversight (i.e. without such a registry).

Option 2: Distinguish between cisgenic and transgenic products

A simpler distinction is whether or not an organism contains transgenes – sequences that would be extremely unlikely (or impossible) to emerge through “traditional breeding” techniques and are found in other species (as commonly produced by GMOs and regulated as such under current laws). This is more easily detected using PCR methods (whilst still requiring sequence information to be shared), but it can provide no information about whether a product has been produced using gene editing. As such, it fails to respond to the needs for labelling, traceability, monitoring and liability associated with GE (as discussed in 12 above).

Option 3: Recognise the difficulties in identifying appropriate criteria and support further research and engagement to explore their implications

Recognising the difficulties in making the distinction between “organisms produced by gene editing or another genetic technology”, which could or could not “have been produced by traditional breeding”, the government should support further research to clarify the matter. Beyond this, recognising that any criteria adopted would have profound long-term implications for consumer choice, food safety, environmental sustainability and food security in the UK and overseas, the government should consider supporting an internationally-networked public engagement initiative to explore these issues amongst publics in the UK and its trade and development partners.

The necessity for the distinction to be scientifically and legally robust may mean that allowing gene edited organisms in UK food and agriculture will be inconsistent with ensuring a high level of protection to public and environmental health. At the same time, there are conditions under which certain gene-edited organisms may contribute (alongside other changes) to forms of UK agriculture that are more productive and have a similar or lower risks for human health or the environment in comparison to existing products. We suggest that further research is needed to identify those conditions (see 'Additional considerations' below).

How to attempt to reconcile these various considerations is a political judgement to be considered by parliament if the government decides to proceed with "legislative change in the next 1-2 years". If the government were to re-define the term 'genetically modified' so as to exclude GEOs by using secondary legislation, in the form of statutory instruments (SIs), then public opposition to such changes would be greater than if primary legislation were used. Changes by SIs would not be seen as democratically accountable, because Parliament would be unable to debate or to amend those SIs.

Section 3 - 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).

The scope of the legislation covered by the questions in this section is so vast that providing a meaningful response to the questions below is impracticable. Beyond that, the binary choice of " yes (sufficent governance)" vs "no (insufficient governance)"does not allow a robust scientific engagement with the complexity of the issues at stake.

14. 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 in the table 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. Please answer Y/N for each of the following sectors/activities:

	Cultivation of crop plants	Breeding farmed animals	Human food	Animal feed	Human and veterinary medicines	Other sectors/activities
Yes (sufficient governance)						
No (insufficient governance)						

Please provide evidence to support your response.

15. 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

Additional considerations

We recommend that careful consideration be given to instituting a mechanism whereby any change in regulations that is introduced is periodically reviewed, in order to assess whether they remain appropriate and proportionate, or require modification, in the light of new evidence and advances in scientific understanding of risks. Relevant questions for DEFRA to consider include when and how such reviews would be triggered and how they would be conducted. Clear objectives for regulation would be needed, and clear criteria would be required to guide expert assessments of changes in the state of scientific knowledge. Some options include:

- Instituting a requirement for precautionary rules to be reviewed at set intervals. This could be done within primary or secondary legislation and on a case-by-case basis. This option would create regular opportunities to review the appropriateness and proportionality of the rules, but it could create some procedural rigidity and bureaucracy.

- Creating a mechanism whereby stakeholders could petition for rules to be reviewed. Applicants could be required to present evidence of a relevant change in scientific knowledge which makes a review necessary. Applications could be presented not only by interested parties (e.g. product developers, commercial entities) but also by independent scientists or public interest groups. Criteria would be required to determine robustly and transparently when a suitable threshold has been reached to trigger review.

- Government could consider commissioning or supporting independent regulatory scientific research specifically designed and properly resourced to investigate areas of uncertainty, ignorance, incertitude and/or risk (Stirling 2010) that have motivated regulations. Reviews could then be performed on the basis of this research.

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