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Submission to the Defra Consultation on the Regulation of Genetic Technologies

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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.

Question 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?

- No – all new plant and animal varieties should be regulated according to the outcomes of the genetic change made and associated farming practices, not the technology used to make the change

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

21st century agriculture faces significant challenges. It needs to provide enough food to meet the demands of a growing and increasingly affluent global population whilst reducing its contribution to the environmental crises of biodiversity loss and climate change. At the same time, agricultural productivity is threatened by these crises. Innovation in the plant varieties and animal breeds available to farmers can help to meet these challenges.

Genetic technologies, including genome editing, can significantly reduce the time and expense of breeding new plant and animal varieties because they enable the introduction of a specific genetic variant into elite plant and animal breeding lines without any loss of the advantageous genetics already in those lines. In the context of crops, where a target gene or genes have been identified, this can enable a reduction in the time required to produce a

new variety from 8-15 years with traditional mutation breeding, to just a few years (Carroll et al., 2016, Miah et al., 2013). As we learn more about the genetic diversity within species and the molecular basis of important traits, genome editing increases the feasibility of introducing some of that diversity into the elite breeding lines for that species (Hua et al., 2019). This can include traits such as increased resilience to pathogens (Zhou et al., 2015, Jia et al., 2017) and extreme weather (Yue et al., 2020).

In the context of farmed animals, genome editing has the potential to reduce harm to animals from current animal husbandry practices (Mueller et al., 2019). There will also be welfare and productivity benefits if genome editing can be used to improve resistance to viral disease (Burkard et al., 2018) or adaptation to abiotic stresses such as temperature extremes (Gratacap et al., 2019).

Genome editing also makes more of the genetic variation within a species available to breeders by eliminating linkage drag (Li et al., 2017). Linkage drag is the phenomenon whereby some genetic characteristics consistently segregate together, so it is much harder to introduce the one without the others. In practice this means a certain proportion of genetic variation is not available to breeders using traditional technologies (Lin et al., 2014). A further advantage of genome editing is the capacity to rapidly combine multiple recessive mutations; for example, when the promoters of three different genes are mutated in rice, resistance to bacterial blight is elevated (Oliva et al., 2019). This would be extremely difficult and slow to achieve in multiple genetic backgrounds by traditional breeding.

The fact that genome editing has these advantages compared with traditional breeding raises a significant question about the interpretation of the phrase “could have been produced through traditional breeding”. Whilst theoretically any combination of variants within the gene pool of a single species could be achieved through selective breeding, and new variants of those genes developed through mutation, especially during breeding in plants, in practice some outcomes are extremely unlikely. This is discussed further in answer to Question 4.

The significance of this for the regulation of genome editing is that traditional breeding products are subject to much less regulatory scrutiny than genetic technology products that are deemed to produce a GMO. This is based on the prevailing knowledge of the 1990s when traditional breeding products were deemed to have a history of safe use, whereas the recombinant DNA technologies used to produce GMOs at that time were feared to potentially present new risks to human health and the environment. Whilst this process-based trigger for regulation was adopted for understandable reasons at the time, extensive global use of recombinant DNA technologies in the intervening 30 years has demonstrated there is nothing inherently risky about using the technologies (Kok et al., 2019). Instead, risk is determined by the genetic change introduced and any resulting change in agricultural practice that this enables, a fact recognised by the risk assessment requirements within the GMO regulatory framework, which serve to characterise the risks associated with the particular genetic change made.

The relevance of this to the question of whether genome editing products should be regulated like traditional breeding products or GMOs, is that this question is predicated on the false assumption that risk is determined by the technology used to make a genetic change rather than the consequences of the genetic change made and the farming system in which a novel trait is deployed. The current regulatory approach has contributed to some environmental harms from the cultivation of traditionally bred crops that might have been anticipated had they been subject to greater pre-approval scrutiny. For example, the cultivation of winter wheat has contributed to the observed decline in farmland birds by removing access to the source of food and shelter that fields left to stubble over winter previously provided (Chamberlain et al., 2000). Similarly, the introduction of dwarf wheat

varieties increased dependency on herbicides, because such varieties are more likely to be outgrown by weeds and therefore less able to compete with them (Chhokar et al., 2008).

Therefore, rather than decide whether genome editing products should be treated like traditional breeding products or the historically over-regulated GMOs, a more evidence-based approach to regulation would consider the outcomes enabled by the resulting organism rather than the technologies involved in its production. The regulatory objective should remain the effective mitigation of undesirable impacts on human health, animal welfare, and the environment, while promoting innovations that address climate change, sustainability, and agricultural productivity challenges. Such a system should be flexible enough to evaluate products arising from new technologies on a case-by-case basis and only to trigger more extensive risk assessment if there is a scientifically credible cause for concern that the resulting product might pose significant risk to human health or the environment. It should also be flexible enough to capture any future breeding method, assuming there is no evidence that such methods are inherently risky.

The challenge for an outcomes-based approach to regulation is determining the thresholds that trigger a regulatory assessment. This is in order to avoid the unnecessary regulation of new plant varieties and animal breeds with low-risk potential. Novelty is one possible trigger and has been used in Canada, but in that context the approach has been criticised for stifling investment in new varieties that might be deemed novel (Smyth and McHughen, 2008, Eriksson et al., 2019). This negative effect is partly a function of the huge costs involved in putting together the dossier of evidence required by GMO regulations. Some of the tests involved, such as rodent feeding studies, provide little added value and conflict with other policy priorities, such as minimising the use of animals in research. Therefore, to ensure the regulatory burden is proportionate to the risk, we recommend the Government undertake a review of how an outcomes-based approach to regulation could work in practice. This should include the outcomes that would trigger a risk assessment and whether some of the current GMO risk assessment requirements are necessary at all or only in some circumstances.

Focusing on the consequences of the genetic change made would also enable greater scrutiny of the purpose for which new plant and animal varieties have been produced, which would help address a range of public concerns connected to the use of plants and animals in agriculture. The use of genetic technologies to help address environmental challenges has been made controversial by organisations campaigning against the use of genome-edited and genetically modified (GM) organisms. Such organisations argue that promises about a wide variety of benefits from the use of genetic technologies, such as improved nutrition or increased drought tolerance, have been made before, but have not all been matched by delivery. There is also a public perception that GM crops are synonymous with the interests of agrichemical companies in promoting high-input agriculture, which is a significant factor in public concerns about the technology (Van Mil et al., 2017). Therefore, as part of an outcomes-based approach to regulation, there should be a public forum in which the rationale and balance of risks and benefits for novel crop varieties are discussed. These discussions would provide useful evidence to regulators as they consider whether new plant varieties and animal breeds are being developed for a purpose that has broad public support.

Question 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?

This question is overly simplistic because it focuses on the technology used to make a change rather than the characteristics of the genetic change made.

With respect to risks from changes to parts of the genome that are unrelated to the trait of interest (off-target changes), genome editing is likely to involve fewer such changes than traditional breeding techniques including mutagenesis. Where such off-target changes do occur, if they have a phenotypic effect, they would normally be eliminated during performance tests of the GE organisms or in backcrossing programs. If they have no phenotypic effect, then they could still be identified using whole genome sequencing, although they are no more likely to pose a risk to human health or the environment than non-editing derived mutations, which occur spontaneously in each new generation. Graham et al. (2020) describes the low potential risk of off-target effects in GE crops.

Gene editing can be used not just to make targeted mutations but also to introduce new DNA sequences at defined positions in recipient genomes. Where genetic technologies, including genome editing, are used to introduce a new gene from a sexually incompatible species, an outcome that could not be achieved with traditional breeding, then there is a greater potential risk of toxicity or allergenicity from the resultant product and this might justify greater regulatory scrutiny compared with traditional breeding products if the source plant had never been in the human diet. Potential impacts on the welfare or environmental impacts of farmed animals in which new sequences have been introduced may similarly be assessed. To be clear, this increased risk is a function of the effect of the genetic material introduced on the phenotype, not the technology used to introduce the material.

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).

In the context of crops and risks to human health, the lack of scrutiny of traditional breeding products has been justified on the basis that such crops have very rarely presented an unanticipated risk to human health (National Academies of Sciences, Engineering and Medicine, 2016, Finkelstein et al., 1994, Patel et al., 2019) and past experience of such risks, for example toxic levels of glycoalkaloids in potatoes (McMillan and Thompson, 1979), facilitates monitoring of such risks by plant breeders. Where genome editing is used to make precise nucleotide insertions, deletions or substitution of one or more genes with homologous regions of DNA from other species that could be traditionally bred with the target species, there is no reason to believe that this presents a greater risk to human health than had that genetic outcome been achieved using traditional breeding. However, it should be noted that producing these genome editing products depends on an intermediate stage that creates a GMO and so any descendants of this intermediate stage would be regulated as GMOs under current regulations. This would not be an issue if the UK were to change to an outcomes-based approach to regulation. The only further consideration with genome editing is the risk of integration of DNA from the editing tools themselves into the target genome. Such an event would be identified through whole genome sequencing and the DNA from the editing tools could be segregated away in further crosses.

With respect to the environment, all agricultural systems impose an environmental impact. Choices made about which plant varieties and animal breeds are used, in which places and

with what inputs determine the type and intensity of those impacts. These interactions are complex. For example, herbicide-resistant crops have led to an increase in the quantity of herbicides used to control weeds (Riley et al., 2011), which subsequently reduces biodiversity, whether in a GM or non-GM crop (Brooks et al., 2021), but have also displaced more harmful herbicides with less harmful ones (Perry et al., 2016) and increased the feasibility of no till agriculture, resulting in benefits for soil quality and carbon sequestration (Cusser et al., 2020). Similarly, traditionally bred, high-yielding crop varieties are dependent on synthetic fertilisers whose production emits GHGs and that may lead to waterway eutrophication (Bailey-Serres et al., 2019), but have increased the amount of food produced from a given amount of land, which should lessen the overall impact of agriculture by reducing the total amount of land required to produce the same amount of food (Balmford et al., 2018). This interaction of plant variety with agricultural practices leading to environmental harm or benefit demonstrates the need for a more systemic evaluation of environmental impact. Greater pre-market scrutiny of known risks would come from an outcomes-based approach to regulation and we also suggest a mechanism in answer to Question 6 for a post-approval monitoring system to identify unknown risks.

In the context of genome editing of animals, there does need to be a consideration of how resistance could drive the evolution of viruses to more virulent and resistant forms, as has been shown to be an issue with vaccination that is incompletely protective against Marek's Disease in poultry (Read et al., 2015). Particular consideration would be required for resistance to zoonotic pathogens, for example avian influenza, because changes driven by resistance could alter pathogenicity in humans (Long et al., 2019). There is a similar risk in crops that new disease resistance could drive evolution of resistance-breaking strains of pathogen. This risk is well known from conventional breeding (Brown, 2015) and could be managed as with conventional crops. It is worth noting, however, that genetically recessive resistance in conventionally bred crops is less easily overcome than dominant gene resistance. This point is relevant because genome editing makes it easier to introduce recessive disease resistance, which will be more durable, though recessive resistance is not currently available for many crop/pathogen combinations.

Question 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

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

Making innovation accessible

Because of the additional costs associated with securing regulatory approval for a GMO, use of these technologies is limited to larger companies. Taking an outcomes-based approach to regulation that is proportionate to risk provides an opportunity for smaller companies and start-ups to get involved in this area, which will increase innovation and the range of crops/farmed animals and countries that can benefit from this technology.

Impacts on trade
Clearly any country or trading bloc that continues to apply a process-based approach to regulation and treats all GE products as GMO will require UK exporters of such products to comply with their regulatory requirements. This will involve such exporters generating all necessary evidence to satisfy the human health and environmental risk assessments for these jurisdictions. A more difficult question is what the impact will be on exporters of non-GE/GMO varieties of a product for which the UK cultivates a GE variety.

Impact on organic agriculture
Under current rules for organic agriculture, it is not possible for a GE or GM product to be certified as organic. There is therefore a theoretical risk to producers of organic products from cross-pollination with GE crops, though this does not apply for tuber-propagated crops. Under current requirements for cultivation of GMOs this risk is mitigated by the rules on co-existence. It is unclear how such risks might be mitigated if some GE products were not regulated as GMOs, but again experience can be gained from countries that do not regulate some GE products as GMOs and have an organic agriculture sector.

Impact on animal welfare
For farmed animals in production systems, animal welfare is regulated through the Animal Welfare Act 2006 and subsequent amendments. This focuses on welfare impacts of production systems rather than any impacts associated with the breed itself; but there is evidence of public concern about the possible use of genome editing in farmed animals based on possible welfare impacts of the genetic change made (Van Mil et al., 2017), although similar concerns have been expressed for animals produced by traditional breeding methods.

Impact on intellectual property
GMOs currently enjoy greater intellectual property protection than new plant and animal varieties/breeds produced using other breeding technologies. This is justified in part by the greater expense of securing regulatory approval for the cultivation of varieties carrying GM traits, but intellectual property protections significantly reduce the accessibility of the benefits of genetic technologies and are a major contributor to public concerns about the commercial use of the technologies (Van Mil et al., 2017). If some GE products are not treated as GMOs, then they should enjoy no greater intellectual property protection than the products of traditional breeding technologies such as plant breeders' rights. The plant breeding industry needs to be able to breed from each other's varieties and it would not be in the public interest if the adoption of genome editing for crop improvement were to compromise the ability of plant breeders to make crosses with each other's varieties.

The intellectual property framework for animal breeders is different as breeders retain control of the genetics of the animals they own.

Consumer choice
Current GMO regulations require any product containing GMOs to be labelled as such. If this requirement is maintained for GE products that are not regulated as GMOs then the label could also include information about the purpose for which GE was used, e.g. “genome edited to be more drought tolerant” as there is extensive evidence that people care about the purpose for which a technology is used as much as the technology itself (Van Mil et al., 2017).

Question 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.

As discussed in the context of Question 1, this question is problematic as there is a difference between what could be produced by traditional breeding in theory and in practice. Criteria should consider the range of mutations that occur naturally over generations. We include below a simplified calculation for genetic variation/generation in a typical hectare of wheat which shows that that in any wheat field, there will be at least one seed that carries a mutation at any position in the genome.

The figures below are calculated by Detlef Weigel (ForMemRS) to illustrate natural mutation rates, based on measured Arabidopsis mutation rates of 1 mutation/0.1Gb/generation.

> *Consider 1 ha of wheat of cultivated wheat.*
> *yield 10 t = 10^4 kg = 10^7 g*
> *weight wheat grain 50 mg = 20 grains / g*
> *Arabidopsis: 1 mutation / 0.1 Gb haploid genome*
> *Wheat: 100 mutations / 10 Gb haploid genome --> 100 mutations per grain*
> *10^7 g --> 2×10^8 grains --> 2×10^{10} mutations*
>
> *2×10^{10} / 2×10^{10} bp --> 1 mutation / bp in every hectare of wheat.*

In crops, mutation breeding techniques using chemical or physical mutagens can also result in larger deletions or chromosomal rearrangements. This means that common mutations such as insertions of one or two bases, single base substitutions and deletions of a small number of bases could all have been produced by traditional breeding techniques.

The challenge for the interpretation of “could have been produced by traditional breeding” is that genome editing enables both highly precise changes, such as the deletion of an exon of CD163 to provide resistance to Porcine Reproductive and Respiratory Syndrome in pigs, and specific combinations of genetic changes that are highly unlikely to have been achieved using traditional breeding. This is reflected in the regulatory framework for genome editing in the US that will be implemented from April 2021 onwards, which excludes combinations of changes from the exemption from GMO regulation for GE products (APHIS, 2020).

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).

Question 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.

Please answer Y/N for each of the following sectors/activities:

a) cultivation of crop plants	N
b) breeding farmed animals	N
c) human food	No comment
d) animal feed	No comment
e) human and veterinary medicines	N
f) other sectors/activities	N

Question 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.

Cultivation of crop plants

As discussed in the context of Question 1, regulation should focus on the outcome of the genetic change made, not the technology used to make that change. This applies equally to crops that incorporate GE events, GM events, or events introduced by any other breeding technology. This regulatory regime should include a public forum to explore the relative risks and benefits of new plant and animal varieties made using genetic technologies. Evidence from a Norwegian public dialogue on genome editing suggests that people are willing to accept greater perceived risks from genetic technologies if they deliver greater perceived benefits (Bratlie et al., 2020). This dialogue included the example of using genome editing to create a blight resistant potato that would be less dependent on fungicides, an application that a large majority of dialogue participants were positive about.

Such discussions should also consider the risks associated with not allowing new plant varieties. For example, one of the most widespread genetic modifications in crops involves the introduction of genes from Bacillus thuringiensis (Bt) to deter insect pests. The protein encoded by these genes is widely used as a crop-spray for insect control by organic farmers (Glare & O'Callaghan 2000). Crops with Bt genes added to them are less dependent on the use of synthetic pesticides or physical barriers such as mesh nets to be protected from insect predation, so one consequence of not permitting the cultivation of Bt crops would be to increase the environmental impacts associated with other forms of crop protection. Whether the benefit of reduced environmental impact from crop protection outweighs the

perceived risk from introducing bacterial genes into crops is the kind of question that should be discussed within the public forum.

Such public discussion is an important component in the trustworthiness of technology governance regimes (Soeteman-Hernández et al., 2021). How such a forum might be run should be included in the review into how an outcomes-based approach to regulation could work in practice proposed in answer to Question 1. This forum should provide a similar function to that of the Human Fertilisation and Embryology Authority in the context of assisted reproduction technologies.

For all new crop varieties, current frameworks do not adequately assess environmental impacts. An outcomes-based approach to regulation would increase the scrutiny of whether new varieties present a credible risk to the environment, and of whether they provide an environmental benefit such as reduced need for agrichemical applications, which might accelerate their approval. There should also be an after-market assessment of whether new crop varieties, however produced, have had unexpected environmental impacts due to the agricultural practices they enable or require. If there were a means by which the environmental impacts associated with a new crop variety and how it is cultivated could be assessed there would be a mechanism for the revocation of approval if it became clear a new variety was leading to an undesirable impact. Such a system could work in a similar manner to the post-marketing surveillance and risk assessment carried out for pharmaceuticals.

Breeding of farmed animals
Much of the thinking done on the regulation of genetic technologies has happened in the context of crops, because this has been the largest market for their application. Genome editing in animals raises distinct concerns compared with crops, such as possible impacts on animal welfare. Current rules on animal welfare focus on production systems rather than the breed itself. As there is currently no framework for assessing the welfare impacts on new breeds, the extent to which this is adequately covered by the current rules governing the use of animals in research should be evaluated. *The Nuffield Council on Bioethics* is currently conducting a review on genome editing in animals and this should inform a wider evaluation of how well existing non-GMO legislation addresses issues raised by the use of genetic technologies in animals.

Human and veterinary medicines
As discussed in the context of Question 2, genome editing in farmed animals needs to be scrutinised for any increased risk to human health from zoonotic disease.

Other sectors/activities
This submission has focused largely on the application of genetic technologies to plants and animals used in agriculture. There are proposed uses of genetic technologies in wild species, including agricultural pests (especially insects) (Nikolay et al., 2019), disease vectors (Kistler er al., 2015), fungi (Liu et al., 2015), micro-organisms (Adiego-Pérez et al., 2019), and wild or invasive species of conservation concern (Phelps et al., 2020). It is unclear whether rules developed in the context of cultivated plants and farmed animals adequately address the risks and benefits of using genetic technologies in wild species. For example:

1) The genomes of non-domesticated species are rarely as completely mapped as crop plants and agricultural animals, and are often more heterogeneous (e.g.

across geographical range). This intrinsically makes it less easy to predict the outcomes of genetic intervention.

2) In these species the notion of "trait" is less useful than in well-known crop species. Not only is the phenotypical diversity not necessarily fully understood and mapped, but the genetic links between physical expression and genetic sequence are less clear.
3) Non-domesticated species (including pests) are free to move. Such species, and their genes, can and do move into a diversity of complex ecosystems, including semi-natural ecosystems whose composition and dynamics are not easy to predict. This is really important in trying to assess the risk of ecological impacts or genetic exchange beyond the target species. Crops therefore offer an overly simple model for thinking about the regulation of genetic technologies, given the range of species for which gene editing is likely to be proposed.
4) In crops it is possible to think of a trade-off between risk and human benefit, since the argument can be made that humanity needs more food grown with less climate and biodiversity impact, and more resilience to climate change. But 'human benefit' is far from easy to specify let alone quantify with non-domesticated species and non-agricultural applications. Public/private benefit (and public/private risk) are issues that become more complicated outside of the context of agriculture.

These examples illustrate the need to think through the suitability of regulations developed in the context of agriculture on a context-by-context basis before non-agricultural applications of genetic technologies can be regulated using the same protocols.

For more information please contact public.affairs@royalsociety.org

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