Defra Gene Editing Consultation: List of questions

January 2021

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.

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.

No - organisms developed using genetic technologies such as GE should not continue to be regulated as a GMO. It makes no scientific sense to regulate GEOs as GMOs so long as the genetic change(s) in question could have been produced by traditional breeding and traditional breeding methods are considered non-GM. **This was the basis for Rothamsted's 2018 field release of gene edited Camelina which was adjudged to be non-GMO by ACRE, setting the clear precedent for future regulation**. Please see "*Advice on genome-edited Camelina plants with increased levels of oleic acid*" https://www.gov.uk/government/publications/acre-advice-camelina-trial.

Mutations occur both frequently and naturally in all living things and exploiting the natural variation in populations that results from these mutations is one of the bases of plant breeding. Since the rediscovery of Mendel's laws, breeders have been crossing plants to create novel genotypes in which these variations are combined. Whilst still successful, this approach is limited by a number of factors, including: the extent of variation that is naturally present; how easy it is to cross parents carrying genetic variations of interest; the generation times of different species; the reproductive systems of the plants (e.g. self-pollinating or outcrossing); differences in ploidy and; recombination frequencies, which vary among species and in different regions of the genome. Since the 1950s, plant breeders introduced ways to overcome these limitations that have become commonplace (See also response to Q3). For example, breeders have increased the variation in their breeding populations using chemical and radiation mutagenesis. These techniques result in thousands of mutations spread randomly around the plant's genome with potential phenotypic effects that are difficult to predict. Despite this, crop varieties carrying mutations induced in this way are used widely without regulation (in the EU they fall under the definition of GMOs but are exempt from the risk assessment and authorisation process applied to plants carrying transgenes). GE also induces mutations, but these are targeted to a specific DNA sequence. GE does not rely on

genetic recombination during meiosis, so can be more precisely targeted, and can be applied in polyploids. Coupled with modern genomics and knowledge of the genetic control of important traits, GE holds out the possibility of producing crop plants with improved agronomic performance, disease resistance, quality and food safety more rapidly than could be achieved by other methods in plant breeding that are in wide used today.

Regarding the regulatory approach, it is in our opinion more appropriate to regulate GE crops as non-GMOs on a case-by-case basis using a product rather than process-based legislation. This approach is similar to what has already been adopted by the USA, Canada, Brazil and a number of other countries (Schmidt et al., 2020). The above-mentioned approach ensures that GE crops, which are free from transgene DNA, do not fall under the GMO regulation solely on the basis that transgenes were used to engineer the intentional and specific change in the genome.

However, what is a matter for a debate is which type of genetic alterations introduced using the GE technology should be classified as non-transgenic. For example, GE crops carrying induced deletions or single nucleotide polymorphisms (SNPs) in their genomic DNA should certainly be exempt from being regulated as GMOs because these types of genetic changes could happen spontaneously or be introduced using chemical or radiation mutagenesis. The situation is less clear when it comes to defining the status of GE crops carrying short DNA insertions or multiple nucleotide substitutions within a genetic locus. As a minimum, it is illogical to classify a GE plant as a GMO if the introduced genetic changes represent an allele naturally present in the gene pool of the engineered crop species, or present in a species that is cross-compatible with it.

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).

For plant breeding, there is no scientific justification for considering the introduction of targeted mutations in a crop by GE to be more risky than either the exploitation of mutations that occur naturally or the generation of random mutations using chemical or radiation mutagenesis. Moreover, the potential to improve the safety of food crops through miniscule precise genomic changes introduced by GE outweighs any hypothetical risk of using the technology. At Rothamsted, for example, we have targeted a wheat gene, *TaASN2*, that encodes an asparagine synthetase enzyme that is active in the grain. Reducing asparagine levels in the grain is desirable because asparagine can be converted during cooking and processing to the toxic contaminant acrylamide. Plants in which *TaASN2* is knocked out with CRISPR/Cas9 (the currently most commonly used GE tool) have reduced asparagine

concentration in the grain but are otherwise indistinguishable from unaltered plants, at least when grown under controlled conditions (Raffan *et al.*, 2021). The edits we induced by CRISPR/Cas9 were mostly deletions, the longest of which was 173 bps, with some single base pair insertions and substitutions. These induced mutations are much smaller than changes naturally found among wheat varieties. For example, we have identified some varieties of wheat in which one of the *TaASN2* genes is missing due to a large (12kb) deletion (Raffan and Halford, 2021). This natural deletion, which is also present in some ancestral wheat species, represents much greater genetic variation than anything we have generated using CRISPR/Cas9.

Rothamsted has also carried out DEFRA-approved field trials of GE Camelina, in which the *FAD2* Δ12-desaturase was inactivated by the deletion of a few base pairs from the specific genes which encode this enzyme. This mutation results in a plant that produces more monounsaturated fatty acids such as oleic acid, which is considered to be health-beneficial (and found in abundance in olive oil). Importantly, the field release of these GE plants at Rothamsted in April 2018 (prior to the ECJ ruling on case 2018C-528/16 in July 2018) was approved by DEFRA on the basis that the mutations they contained were indistinguishable from mutations that occurred naturally, and on that basis these GE plants were not classified as GMOs (https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/800593/gmo-camelina-oleic-acre-advice.pdf.pdf). Thus, the precedent for regulating GE plants differently from GM plants has already been established by DEFRA and ACRE, and we would propose that this example be used as the model going forward (Faure & Napier, 2018). If the UK national regulatory body previously indicated that GE is not within scope for regulation as a GMO, then now that we have left the EU and should not be legally constrained by rulings from the ECJ, it is logical and sensible to return to the previous UK specific position.

There is potential for GE to provide an invaluable resource in disease resistance in crop plants. The simultaneous editing of the three *TaMLO* homologues in bread wheat, for example, improved resistance to powdery mildew (Wang et al., 2014). An analogous strategy was successfully used in tomato: the CRISPR-edited tomato line carrying a deletion in the *SlMlo1* gene showed enhanced resistance to the powdery mildew pathogen (Nekrasov *et al*., 2017). Another example is the CRISPR knockout of the ERF transcription factor gene *OsERF922* in rice that reduced susceptibility to rice blast (Wang *et al*., 2016). Furthermore, GE can be particularly useful in plants with long reproductive cycles and/or trees that rely on vegetative propagation, such as in citrus (Jia *et al*., 2017), coffee (Breitler *et al*., 2018), grape (Nakajima *et al*., 2017) and apple (Nishitani *et al*., 2016). The CRISPR GE technology could be used to recreate naturally occurring genetic polymorphisms, which enhance a particular agriculturally important trait in a desired genetic background (e.g. a specific elite cultivar).

In conclusion, crops produced using the GE technology definitely do not pose a greater risk to the environment or human health as compared to traditionally bred crops. Perhaps the risk is even lower in the case of GE crops as the GE technology is much more precise as compared

to conventional forms of chemical or radiation mutagenesis and, as a result, the phenotypic outcomes of GE-mediated targeted mutagenesis are far more predictable. As mentioned above, the regulatory approach cannot be the same for all GE applications and lack of transgenic elements or DNA from a different species in the final product should be a pre-requisite for granting an exemption from being regulated as a GMO.

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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

Regulating GE crops that carry gene edits that are indistinguishable from naturally-occurring mutations will be impossible, especially as GE and GM crops are not being regulated by major exporters of crop products, such as the USA. Nevertheless, it seems likely that the EU will move slowly on updating its GMO regulations in response to any changes in the UK's position. There may, therefore, be difficulties in exporting GE products to the EU, at least in the short term. However, the EU already imports millions of tonnes of GM soybean, maize and cotton every year, and it is much easier to obtain approval for the import of biotech crop products into the EU than for cultivation therein; this is the situation that UK producers are now in. So exporting GE products to the EU will not be impossible. At the same time, there is the opportunity to bring UK regulations on GE crops into line with our other major trading partners, including the USA, Canada, Australia, China, Japan, Argentina and others.

The argument usually follows that GE can lead to off-target mutations whose consequence cannot be predicted and may be harmful to public health, nature or the environment. The scientific literature does support the contention that gene editing can lead to rare off-target mutations BUT traditional breeding methods lead to the introduction and combination of many more off-target mutations. Indeed, off-target mutations with unpredicted consequences occur continuously in all life and permit evolution. Virtually no two individual organisms are genetically identical. If we had a regulatory system that required no off-target mutations (absolute genetic uniformity), we would have to test every individual we ever release into the environment, irrespective of the methodology that was used to produce it. All organisms that are bred, released into the environment and used for food and feed must be regulated, but off-target mutations are no justification for treating GEOs differently from traditionally bred organisms.

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 we state above, mutations occur naturally and frequently in all living organisms and these mutations define "natural variation" and allow for adaptation and evolution. Natural genetic changes include point mutations that result in single nucleotide polymorphisms (SNPs), insertion or deletion of longer segments of DNA (INDELS), and even major structural changes where DNA may be exchanged between chromosomes. Some crop species show evidence for introgression of DNA from other species; from rye into wheat, for example (Cheng *et al*., 2019; Johansson *et al*. 2020; Hao *et al*., 2018). The genomes of many species also contain transposable elements: segments of DNA that naturally and randomly move around the genome. Indeed, the large deletion in wheat encompassing a *TaASN2* gene that we discuss above is adjacent to a transposable element (called Ty1-copia), which may explain how this deletion occurred. Many sweet potato genotypes naturally contain DNA from nature's genetic engineer, *Agrobacterium tumefaciens* (Kyndt *et al*., 2015). Several crop species have also undergone whole genome duplication or, like bread wheat, have become polyploids as a result of species hybridisation and genome doubling (Guo *et al*., 2019). Without genetic change, evolution by natural selection would not occur, and there would be no variation for plant breeders to exploit for crop improvement by the 'traditional' crossing of different genotypes. It is also worth noting that the concept of a single unique genome sequence defining a species is now an outdated model; instead, the pan-genome concept (in which only a discrete subset of any individual organism's genetic code is common to other related individuals of the same species) indicates that the NGO concept of "sanctity of the genome" is a misunderstanding and gross simplification of modern molecular biology.

Against this background, the changes typically induced by GE techniques are relatively minor and are therefore within the scope of what can and does happen naturally. The sweet potato example above demonstrates that even the insertion of long segments of DNA from sexually incompatible species could be viewed as something that can and does occur naturally. Although novel applications of GE may need to be regulated and carefully considered, the basic use of the technology does not produce organisms that could not potentially have been produced by traditional breeding.

The notion that there is such a thing as 'traditional breeding' is also questionable. Mendel's laws, which underpin scientific plant breeding, were rediscovered in 1900. F1 hybrids (controversial at the time) were first marketed in the 1920s and 30s, crops carrying mutations induced by chemical or radiation mutagenesis in the 1950s, Triticale (an artificial wheat/rye hybrid produced in a lab) was released in 1969, the first commercial GM plant was marketed in 1994, and doubled-haploids started to be used to generate mapping populations in the 2000s, relying heavily on modern genomics and the nucleotide sequencing of entire plant genomes. So what is 'traditional' breeding?

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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).

1. 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 *[Y/N] Not our area of expertise*

c) human food *[N]*

d) animal feed *[N]*

e) human and veterinary medicines *[Y/N] Not our area of expertise*

f) other sectors/activities *[Y/N] Not our area of expertise*

Please provide <u>evidence</u> to support your response

2.

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).

It is entirely appropriate that formal regulations are drawn up to cover the development of new technologies. These should ensure the public's safety and encourage public confidence that all the necessary precautions are being taken. However, it is important that such regulations are grounded in the science and that their management after adoption is also science-lead and enabling. As outlined above, and in stark contrast, the current EU position on the regulation of GE as GM is entirely out of step with the rest of the world, despite the plethora of evidence for adopting a different position. Going forward, the UK should ensure a process for GE and GM approvals within an appropriate and beneficial UK regulatory framework, handled in a timely manner. Otherwise, development of the technology will simply be stymied, as has happened for GM crops and looks likely to happen for GE crops in the EU27. We should not let our innovations similarly wither on the vine.

The regulation of GM crops in the EU is covered by Directive 2001/18/EC of the European Parliament and Council on the deliberate release into the environment of genetically modified organisms (GMOs), together with GM Food and Feed Regulation (EC) No. 1829/2003, which was adopted in 2004. An organisation applying for a Part C consent to cultivate a GM crop in the EU must provide detailed information on the host plant species, as well as the nature of the genetic modification it carries and the methods used to bring the modification about, as well as an environmental impact assessment. Guidance can be found in the Codex Alimentarius, the annex to Commission Implementing Regulation (EU) No. 503/2013 and Directive (EU) 2018/350 (a recent amendment to Directive 2001/18/EC). Each application is assessed by the European Food Safety Authority (EFSA) GMO panel. If the GMO panel's opinion is favourable, the application is voted on by the Commission's Standing Committee on Plants, Animals, Food and Feed (PAFF), with representatives from all Member States, using a Qualified Majority Voting system. To date, a quarter of a century after GM crops were first grown commercially in the USA, only two GM crop varieties are currently approved for cultivation in Europe: MON810, a variety of insect-resistant (Bt) maize developed by Monsanto, as well as some derivatives produced by local breeders under licence from

Monsanto, and the Amflora potato produced by BASF. Amflora was engineered to optimise its starch for industrial uses. Despite the usefulness of this product, it spent ten years in the EU's approval process and although it was finally approved in 2010, BASF ceased plant biotechnology activities in Europe in 2012 (partially in response to the delays in approval) and Amflora is no longer available anywhere. Efforts to develop new GM crop varieties for cultivation in the EU or elsewhere in Europe have now been abandoned by biotech companies: there have been no applications for approval to cultivate a new GM crop variety in the EU for over a decade. Instead, companies are focussing on obtaining permission for food and feed use without seeking approval for cultivation. This means that European farmers are competing with GM crops but are unable to use them. Equally, European consumers are happy to consume billions of meals derived from animals fed GM ingredients. This has been discussed in greater depth by Halford (2019). Collectively this indicates the dysfunctionality of the current EU approach to regulation of GM and GM-derived products – on one hand ensuring a de facto moratorium on cultivation, and on the other hand, importing millions of tons of GMOs and GM-derived products. It is critical to the UK's innovative agriculture sector that we learn from this example and do not take a similar path. Contrary to suggestions from lobby groups, it is the EU which is out of step with the rest of the world, and such a stance is not based on science or evidence (Dima & Inze, 2021)

We therefore support the drawing up of bespoke and distinct regulations for GM and GE to cover their use in crops, food and feed. However, it is imperative for the sustainability of UK farming, plant breeding and the crop research that underpins it that such regulations are evidence-based, science-driven and enabling, also in a way that allows the technology to develop. They should also serve to enable trade with the very many countries which embrace these technologies.

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