Part 1: The regulation of GMOs 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?

No – they should not continue to be regulated a GMO

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

Fera's position is that gene edited organisms should not universally be regulated as genetically modified organisms (GMOs). Further to this, Fera would recognise two positions for GE organisms, based on demonstration of equivalence to traditional breeding, i.e.:

1. Gene-edited organisms would not be regulated by the GM regulations where it is shown that the resultant organism could, with reasonable certainty, have originated by traditional breeding.

OR

2. Gene-edited organisms would be regulated by the current GM regulations where it is shown that the resultant organism could, with reasonable certainty, not have originated by traditional breeding.

Of these positions, Fera would advocate for position 2). For clarity, this is not limiting regulations to be applied to GE organisms that fulfil the definition of a GMO, but where an organism could not reasonably have originated by traditional breeding (within a finite time). By example this may include 'accelerated breeding' for multiple traits.

We note that, whereas the identity of GE organisms can be identified by the presence of the introduced gene edited sequence (mutation), this is not a test for the method of mutation i.e. such a mutation may have originated by traditional breeding. This differs from GMOs where the mutational event invariably inserts 'foreign DNA' and therefore provides both a test for identity and the method of breeding. We state this as presenting a fundamental difference in how GE, GMO and traditionally bred organisms may be identified to their method of development. We observe that, where a regulation is applied to demonstrate equivalence of difference between GE and traditional bred organisms, then evidencing that position is intrinsically hard and likely to involve some subjectivity. This is discussed further in 2.4.

The fitness of this regulatory position would be dependent on the undertaking of 'good practice' amongst all practitioners of gene editing as an essential provision in building trust over the appropriate use of the technology. Fera would strongly advocate for provision of a regulatory and/ or industry standard that sets out minimum working practices for the development and documentation of the GE organisms, such that an independent body would have high confidence that the GE organism is as described. This may be akin to the Good Laboratory Practices associated with agri-chemical (pesticide) development and registration.

We support the above statements by the following technical points:

1. On the basis that genetic changes across the genome caused by gene-editing are equivalent to those by traditional breeding, we consider that they should be regulated in the same way.
2. We consider that there are insoluble practical problems with the current regulation of all gene edited organisms as GMOs. In our view, it is not possible to develop a method to universally detect GE organisms, as GE does not leave a foreign DNA element within the genome in the same way that conventional genetic

modification does (e.g. presence of promotor regions). It may be possible to develop methods to detect specific GE organisms, such as an assay which directly detects the presence of the GE change, but this does not conclusively 'prove' the organism has been generated by gene editing. A wider discussion of this issue can be found here: https://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf (ENGL 2019, Detection of food and feed plant products obtained by new mutagenesis techniques).
Moreover, under Regulation (EU) No 503/2013 (which has been transferred into UK legislation), an analytical test to detect a genetically modified organism requires that the test "shall be specific to the transformation event (hereafter referred to as 'event-specific') and thus shall only be functional with the genetically modified organism or genetically modified based product considered". Where an organism has been gene-edited to contain a DNA sequence that is already found in that species, it will not be possible to develop an analytical test that fulfils this 'event-specific' requirement. This lack of reliable detection methods makes regulation of particular gene edited organisms problematic, as regulation requires the ability to detect the regulated organism.

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?

Not Answered

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).:

We consider that GE has a potentially higher risk of intended harm than traditional breeding due to its relative accessibility (measured by lowering technical barriers for undertaking GE research and increased fidelity for manipulation), but we do not consider that as intended within the scope of this consultation.

We identify that risks to the environment or human health are likely to arise from (a) the intended gene edited event itself, (b) from off-target mutations elsewhere in the genome, and from pleiotropic effects arising from either (a) or (b).
1) We do not consider an intended DNA mutation arising via gene editing to be in anyway different from a mutation arising by another means, where the two produce identical DNA sequences. We therefore consider the risks to be the same for this 'type' of mutation.
2) We expect pleiotropic effects to be similar between organisms produced by traditional breeding and by GE.
3) We assume that the risk from off-target mutations is related to the location of those mutations (e.g. coding region versus non-coding) and to the number of those mutations. We are not aware of any definitive study that compares qualitatively, quantitatively or functional differences associated with off-target mutations as driven by GE and traditional breeding. However, we do expect off-target mutations to be lower, and to that extent we expect the risks to be lesser. As a sound knowledge of off-target mutations by GE and traditional breeding is central to estimates of equivalence, this area should be a research priority for enabling effective development of GE technology.

Related to 3, we would wish to see agreement on appropriate good practice and oversight on the degree to which GE technologies must seek to avoid off-target mutations. Examples of practices that can reduce off target mutations include the use of stringent guide RNAs, the use of Cas endonucleases that have been

modified to be more specific, avoiding methods that cause double stranded breaks in the DNA, and the use of delivery systems that will only be present transiently in the cell (e.g. the use of RNA or ribonucleoproteins).

Although not a direct result of the process of gene editing itself, we consider that rapid and widespread adoption of gene edited crops and livestock could have additional effects. These may impact the overall genetic diversity within particular species (e.g. a narrowing of genetic diversity due to heavy use of one cultivar, or a widening the overall genetic diversity as traits are transferred between cultivars without back-crossing and a wider range of cultivars are used).

We further note that that rapid and widespread adoption of gene edited crops and livestock may impact public opinion and perception of gene editing.

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

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

Trade: Yes. A change in the UK position on regulation as described would have trade implication on overseas export markets that regulated GE organisms as GMOs and where supply chain integrity cannot be assured, or accepted, by the importing nation. We would expect that a UK exporter would need to make a claim of goods being “free of GE material” to be accepted by the importing nation.

Consumer choice: Yes. If GE goods are not labelled under the GMO regulations, then the consumer would not be able to exercise a right of choice to purchase, or not purchase, GE products. It is likely that some sectors will take an ethical position to be “GE-free”, akin to the position for GMOs; whereas, in examples were GE delivers benefit (e.g. nutritional or environmental) a preference to buy GE products could prevail. The market price of ‘with GE produce’ or ‘free-from GE produce’, could need regulation to ensure any price premium associated with the GE status did not disadvantage sectors of society wishing to purchase on that basis.
We consider that public opinion should be used to guide the choice over whether to require GE goods to be labelled.

Regulation: Yes. In the provision of supply chain integrity – from input, to farmer’s field, to consumer – we observe the inherent difficulty associated with detecting GE organisms where the absence of a foreign DNA marker, as with GMOs, makes direct detection more challenging. Therefore, the deployment of regulation based on detection of GE for assurance of absence/ presence is likely to be problematic. Supply chain integrity (Stewardship) as a partnership between government and industry will therefore be fundamental to underpinning any labelling of the GE status on goods.

Animal Welfare: We consider that gene editing can offer significant animal welfare benefits (e.g. disease resistance, ‘poll-less’ cattle) which will be more
wide-spread in the UK if gene edited organisms are removed from GMO regulations. However, we note that these benefits would not be a direct result of gene editing as a tool, rather a result of the wise use of the tool.

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Environment: We recognise that use of GE organisms for agricultural and environmental purposes would be associated with environmental impacts. On a
case-by-case basis, such impacts could have a net benefit, neutral or negative outcome. Examples of potential beneficial impacts could be the reduced need for pesticides. Possible negative impacts could be spread of the gene edited genetic material into other plant species that may compromise a GE free status.
In the event that GE organism were not regulated as GMOs, we are not aware of any current regulatory approval pertaining to the release of traditionally bred livestock or crops under which an environmental impact assessment of GE organisms may fall. Under section 3.2 we advocate that an environmental assessment is considered for certain GE and traditional bred organisms prior to commercial release (see section 3.2a).

Intellectual property: We anticipate that the way that Intellectual Property is regulated for gene edited organisms will be different if they are removed from GMO regulations.

Commercial exploitation of gene editing: Current regulations that recognise GE and GMO products as the same present a high cost to industry for market access of new products based on such technologies. This barrier is especially steep for small and medium sized enterprises. Were gene edited organisms to be removed from the GM regulatory control to fall within the current regulation of traditional breeding, then this would enable a greater diversity of businesses to exploit gene editing technologies.

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 question falls outside Fera's areas of core expertise. However, our view is that there is no clear-cut answer to this question as the genetic changes produced under traditional breeding are not themselves defined. Therefore, where the distinction is drawn between could/ could not have been produced by traditional breeding will be very difficult to decide upon. Below we briefly discuss two distinct routes to the acquisition of genetic novelty, with examples that we consider to be equivalent to traditional breeding:

- Mutations similar to 'background' mutations. Most individual single base pair substitutions could arise by natural processes, given sufficient numbers of generations and individuals. Therefore, a single point mutation that has been introduced through gene editing may equally have been produced by traditional breeding.
- Under traditional breeding, organisms acquire genetic novelty (through breeding) which creates new combinations of genes in the offspring. This process can be mimicked by gene editing by recreating a single trait from one cultivar or breed in another. We consider that this type of gene editing is sufficiently similar to traditional breeding to be considered as "could have been produced by traditional breeding". For example, the recreation of a genetic change that is present in one tomato variety into another. The extent to which the degree of genetic change caused by gene editing (multiple base pair changes, multiple traits) is acceptable will be difficult to establish.

However, this becomes increasingly subjective when discussing more complex examples, such as the introduction of multiple individual single base pair changes, multiple traits (e.g. analogous to the concept of GMO gene stacking) or complex traits that could have arisen individually by natural mutation, but are very unlikely to have arisen simultaneously. Due to this subjectivity and the novelty of the technology, we would advocate for an intitial precautionary approach to deciding these criteria.

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While the focus of the above is of 'on-target'/ intended mutations, we note that off-target mutations will occur. Consideration should be given as to whether these are gene-editing 'events' in their own right or can be excluded from consideration.

Part 2: Questions on broad reform of legislation governing organisms produced using genetic technologies

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:

Gov_Sufficiency - Yes (sufficient governance):
Human food, Animal feed

Gov_Sufficiency - No (insufficient governance):
Cultivation of crop plants, Other sectors/activities

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.:

Our interpretation of the question is that this runs the scenario where GMO regulations are lifted and asks to what extent a status quo could be maintained (or 'lost') through better use of other mechanisms (regulatory and non-regulatory).

a) cultivation of crop plants
The following presents a position for a Strategic Environmental Assessment (SEA) Gateway for new varieties, crops and regulated agronomic practices. Currently, regulations pertaining to new variety release by traditional breeding, are overseen by DUS and VCU that do not encompass a rigorous assessment of environmental outcome. We also note that the cultivation of a new crop, or agronomic practice, does not require an environmental risk assessment. We contrast this regulatory position to the registration of a new pesticide or its novel application, where an environmental impact assessment is required. In this we observe that the registration for the cultivation of a GMO crop is closer to the release of a pesticide than a new crop variety or crop. Some of the largest environmental impacts of the UK, and globally, over the past 100 years, the green revolution, have been driven by changes brought about by traditional breeding and/ or agronomic practices. For the UK we have breeder examples of short strawed or winter sown cereals. The cultivation of oil seed rape, over the past ~50 years, has risen from ~4,000ha in 1970 to 530,000ha in 2019, with a max of

~750,000ha in 2012; whereas maize cultivation for fodder has increased from ~17,000 ha in the early 70s to under just under 200,000ha in 2017.
If Defra is to realise the ambition of its 25 Year Environmental Sustainability policy, then a review on the regulations and incentives pertaining to the release of new varieties, new crops and new agronomic practices should be considered. This would logically provide a single gateway for new varieties, crops and agronomic practices to gain 'market entry' based on the outcomes they deliver, and not the technology.
In this scenario traits considered as environmentally novel, akin to novel food, or hazardous may trigger a higher requirement. In the example of crops, we consider that 'novel traits' are phenotypic traits:

- that are not already present in that particular species under cultivation in the UK;
- that are existing and heavily exaggerated compared to other species under cultivation in the UK;
- that are absent when universally present in that particular species under cultivation in the UK.

Special consideration would also be given to traits that are deemed as potentially hazardous e.g.
that confer a phenotypic trait that may enable the crop to establish wild populations (e.g. extend its climatic tolerance or growing conditions, express herbicide resistance);

- Uptake of the trait in wild species by natural crossing;
- that may negatively affect wildlife or biodiversity (e.g. by expressing a novel or upregulated plant defence chemical toxic to invertebrates);
- that create step changes in agronomic practices (e.g. increased requirement for water);
- that affect how particular genetic sequences are inherited in the population (e.g. gene-drive type systems).

c) human food
Safety risks from consumption of GM/GE food could be regulated for under the Novel Foods licencing process using the substantial equivalence framework (demonstration of substantial equivalence to a non-GM/GE). This regulation sits with the UK Food Standards Agency.

d) animal feed
The desired regulation on GM feed has become increasingly difficult to enforce given the dependency on soya and the ubiquitous cultivation of GM soya, over non-GM varieties, in countries where supply chain integrity is not assured for GM. In the UK supply chain, it is accepted that feed containing soya contains GM soya.

f) Other. We consider that consumer choice (labelling) for GMO-free would be maintained as an ethical right of choice for as long as the consumer wishes so to do, and that Government and/ or industry should protect that position. This same logic would apply to GE organisms should consumer opinion to be voiced as requiring GE to be labelled. This is a position of ethics and market viability, rather than science when the impacts of food safety and environmental impact are assumed as satisfied.
As set out in question 2.1 we observe that there are difficulties in universally detecting gene edited plants and animals from field through to processing and
end-products. This aspect of GE makes enforcement of regulations highly problematic. In the absence of being able to monitor for GE, an industry/ governmental stewardship scheme that provided supply chain integrity and a choice to consumers over traditional, GE and/ or GMO should be considered. Such a scheme would prove equally applicable to GMOs in support of supply chain integrity and consumer choice

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