Written evidence submitted by the Advisory Committee on Releases to the Environment (ACRE) (GEN0039)

Executive summary:

- ACRE is an independent committee that provides statutory, scientific advice to UK ministers on the environmental safety of GMOs, principally through case by case risk assessments of individual GMOs. We work to EU and national legislation on the deliberate release of GMOs into the environment and as such, our response to this inquiry focuses on Question 2 and therefore on genome editing.
- For the majority of organisms produced by genome editing it is unclear whether the EU's/ UK's definition of a GMO applies to them. It is only clear in cases where DNA from other species has been inserted into the organism's genome (as opposed to changes to the genome that could have occurred naturally); these organisms will be captured by the GMO legislation.
- This lack of regulatory clarity is the result of countries (including the EU) having adopted regulatory frameworks that, at least in part, capture organisms based on how they were produced (i.e. a so-called 'process-based' approach to regulation). The EU also places undue focus on alterations/ variations to the genome rather than on the novel characteristics of the organism. This is unhelpful as evidence from genomic studies shows that genomes exist in highly plastic and variable states between and within individuals; in some instances such variants may have virtually identical biochemical and physical characteristics.
- We argue that a trait-based (also referred to as a product-based) approach to regulating novel organisms would provide a more consistent and future-proofed approach. This is particularly important because the technology is developing so rapidly.
- Organisms containing gene drives are GMOs and gene drives have generated a large amount of interest in recent years. It is a significant issue on its own and it may be helpful to encourage separate discussions on topics such as genome editing, gene drives and synthetic biology so that they are not confused.
- We monitor scientific developments and discuss reports on regulatory issues associated with the potential release of organisms containing gene drives into the environment. Our principle interest is whether and to what extent the current approach to risk assessment would be effective, noting that scientific (as opposed to social and economic) issues associated with adverse impact on human health and the environment are captured by the risk assessment. We consider that the current risk assessment would be fit for purpose i.e. it would enable us to identify plausible risk hypotheses. The challenge will be to establish what information will be required to identify and characterise these risks and how it can be generated in a stepwise manner prior to full-scale environmental release.

ACRE's response to Question 2

ACRE is an independent committee that provides statutory, scientific advice to UK ministers on the environmental safety of GMOs, principally through case by case risk assessments of individual GMOs. We work to EU and national legislation on the deliberate release of GMOs into the environment and as such, our response to this inquiry focuses on Question 2 and therefore on genome editing.

Written evidence submitted by the Advisory Committee on Releases to the Environment (ACRE) (GEN0039)

1) Genome editing

1. Genome editing refers to a suite of techniques that are used to make targeted changes in the genetic code of organisms. These involve the use of site-directed nucleases (SDNs), which cut DNA at specific sites (so-called 'molecular scissors'). Examples of SDNs include zinc finger nucleases (ZFNs), transcription activator-like effector-based nucleases (TALENs) and the CRISPR-Cas system. CRISPR/Cas has been the most commonly used of these techniques because of its versatility in recent years. The PostNote cited in the call for evidence provides helpful examples of its application in different sectors e.g. agriculture and medicine.

2. Some organisms produced by genome editing techniques will be captured by the GMO legislation controlling the deliberate release of GMOs into the environment (i.e. Directive 2001/18/EC). This will be the case if DNA from another species is inserted into the sites cut by the SDNs, except in the case of human beings, who cannot be classified as GMOs. In all other cases, it is not clear whether the GMO legislation applies or not; this includes organisms containing changes to their DNA, which could have occurred naturally or by conventional techniques. In our advice on 'New Techniques in Plant Breeding'[1], we argued that there was a strong scientific case for concluding that the EU's definition of a GMO does not apply to organisms produced by genome editing techniques if these edits could have occurred naturally or by conventional breeding. Ultimately, it will be a legal decision that determines whether Directive 2001/18/EC captures organisms produced by genome editing. We are aware that the European Court of Justice will be considering a question relating to the regulatory status of organisms produced by such techniques.

3. After producing our report on New Techniques in Plant Breeding, we produced a paper[2] that considered why the EU's definition of a GMO is problematic to interpret and how this could be improved. We concluded that a definition which is, at least in part, process-based (i.e. focuses on the techniques used to produce an organism) will be open to interpretation and difficult to future-proof. Rapid developments in genetic technologies since the Directive was first adopted have made this more apparent.

4. Evidence from genomic studies has established that genomes exist in highly plastic and variable states between and within individuals; in some instances such variants may have virtually identical biochemical and physical characteristics. A recently published paper by Krasileva et al. (2017)[3] describes the considerable genetic variation present in wheat, for example. The fact that genomes are so variable and that these differences may not lead to changes in the characteristics of these organisms calls into question the logic of the legislation's focus on genomic alterations rather than on the novelty of an organism's characteristics when defining whether it is a GMO or not.

---

[1] ACRE advice: New Techniques in Plant Breeding. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239542/new-techniques-used-in-plant-breeding.pdf

[2] ACRE advice: Why a modern understanding of genomes demonstrates the need for a new regulatory system for GMOs. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239852/genomes-and-gm-regulation.pdf

[3] Krasileva K.V., Vasquez-Grossa H.A., Howella t., Bailey P., Paraisoa F., Clissold L., Simmonds J., Ramirez-Gonzalez R.H., Wanga X., Borrill P., Fosker C., Ayling S., Phillips A.L., Uauyd,C. and Dubcovskya J. 2017. Uncovering hidden variation in polyploid wheat. www.pnas.org/cgi/doi/10.1073/pnas

5. On this basis, we have suggested a different approach i.e. a definition / regulatory trigger that takes account of the novelty of the final product. This would be independent of newly-arising and currently unforeseen technological developments and it would focus on identifying and characterising the risk of harm associated with the novel characteristics.

2) Gene Drives

6. The discovery of the CRISPR/Cas system in bacteria and its application as a tool for gene editing has facilitated the development of organisms containing gene drives (as described in the POSTnote).

7. These organisms would be captured by Directive 2001/18/EC because DNA from another source is inserted into their genomes. Our interest is in whether the current approach to risk assessing GMOs is fit for purpose in this context. There has been a great deal of discussion on this topic within the last three years and our understanding at this point in time is that the systematic approach we use is appropriate. The issues raised in discussions about the safety of releasing organisms containing gene drives are issues that are considered in GMO risk assessments more generally, although the context will vary depending on the particular case. These include considerations about potential effects on the modified organisms themselves and how they will affect environments into which they disperse, including impacts on other species; the potential for, and impact of, vertical and horizontal gene flow etc. The challenge will be to establish how to address such questions and establish what is acceptable and not acceptable in terms of potential impacts on the environment.

8. Evidence produced to address such risk-based questions will need to be generated throughout the process of development. The GMO regulations foresee a step-by-step approach whereby environmental exposure is increased if uncertainties about risk of harm are addressed satisfactorily. The USA's National Academies of Sciences (NAS), Engineering and Medicine 2016 report on '*Gene Drive Research in Non-Human Organisms: Recommendations for Responsible Conduct*'[4] also endorses this approach. We could conceive, for example, that a GMO with the desired trait but without the associated gene drive might be released into the environment as a preliminary step in order to gather information.

9. It will be extremely important to establish what constitutes unacceptable harm from the outset. This can be informed by scientific evidence/ knowledge but it also has a social dimension (e.g. the acceptability of introducing genetic systems that may be designed to persist in populations or the acceptability of eradicating a species). Otherwise, there may be a tendency to attempt to address this lack of consensus on what constitutes harm by collecting more data / focusing on hazards; such a process is potentially an open-ended exercise. Public engagement and communication between developers and regulators will be crucial.

10. Another issue with the current regulatory framework for GMOs, which is likely to be particularly relevant to organisms containing gene drives, is that it does not explicitly take

[4] http://nas-sites.org/gene-drives/

benefits into account. Implicit in an approach that takes benefits into account, is the idea that a certain impact might be tolerated when the benefits are high, whereas they might not be if the product had much more restricted value. We consider that a regulatory system that takes account of the potential benefits and the consequences of not authorising a product and which includes compensatory measures (where appropriate) has the potential to deliver greater overall benefits.

11. We are following the issue closely and are holding a joint meeting with our colleagues on the scientific advisory committee dealing with GMOs under contained use conditions (SACGM) in March, 2017 to consolidate our understanding of the current state of the art and the suitability of our risk assessment framework.

January 2017