ADVISORY COMMITTEE ON RELEASES TO THE ENVIRONMENT

Report 3: Towards a more effective approach to environmental risk assessment of GM crops under current EU legislation

Executive summary and recommendations

In this report we explore how the EU's legislation that controls the deliberate release of genetically modified organisms (GMOs) into the environment may be interpreted in a way that promotes a broader and more effective approach to using evidence when framing and addressing risk-based questions associated with applications to cultivate GM crops. This in turn will support more cost-effective, efficient and informed decision-making.

The deliberate release of GM crops for cultivation is controlled by Directive 2001/18/EC. This legislation requires decisions on whether, and under what conditions, a GM crop can be authorised to be based on a scientific, case by case estimation of the overall risk to human health and the environment. It requires risks (a function of hazard and likelihood) to be characterised by comparing characteristics of the GMO (and its use), which have the potential to cause adverse effects, with the characteristics of the non-GM line from which it was derived.

The Directive provides applicants with the flexibility to submit evidence to address risk hypotheses on a case by case basis, taking into account crop type, nature of the modification, scale of the release and experience of growing the GMO in other parts of the world. However, environmental risk assessments (ERAs) are becoming overly formulaic. As a consequence, there is a tendency for them to contain information that does not help inform decision makers about the risk of adverse effects occurring. The situation could worsen if regulators undermine the case-by-case approach by stipulating prescriptive evidence requirements in ERAs to cultivate GM crops.

The legislation establishes that ERAs should address only those consequences of GM crop cultivation that have the potential to cause adverse effects. ERAs should also be based on defined hypotheses of how an adverse effect might arise from the GM crop under field conditions. The lack of any link between a characteristic of a GM crop and an adverse effect leads to open-

ended data gathering exercises. This is also a consequence when ERAs focus on hazards rather than risks, because hazard-based assessments do not take the likelihood that an adverse effect will occur into account. They can also result in superfluous recommendations for risk management measures.

The EU's approach to dealing with GM stacked events is an example of where well-defined risk hypotheses linking characteristics specific to the GMO and adverse effects are lacking. Except for in a small number of foreseeable cases, there is no a priori reason to assume that crossing individual GMOs will result in novel characteristics that would cause additional adverse effects. In such cases, the risk is no different from that of the individual GMOs considered separately. Repeating studies previously carried out for single events is not necessary with stacked GM events unless clear, hypotheses-driven pathways to adverse effects are identified.

In addition to assessing the risks associated with the intended changes made to a GM crop, an ERA must also address the possibility that unintended changes could occur that cause adverse effects. In the absence of a plausible link between a characteristic of a GM crop (and its use) and adverse effects, there is the potential for open-ended evidence-gathering exercises. Where an adverse effect is defined but there is no apparent link to a characteristic of the GM crop or its use, we recommend that a weight of evidence approach is adopted. This involves utilising wider evidence effectively including information on the cultivation of the GM crop elsewhere in the world. It may also use specific data on the molecular, phenotypic and agronomic characteristics of the GM crop. If there is evidence that an unintended change has occurred and this can be linked to the adverse effect, a structured approach to characterising the risk should be carried out (Fig.1). In practice, the scrutiny associated with the breeding process is likely to remove plant lines with unwanted, unintended characteristics. Requirements for data from tests when the weight of evidence indicates no reason to link an adverse effect to a GM crop are unhelpful.

Whereas ACRE recommends a weight of evidence approach to identify known adverse effects resulting from unintended changes to a GM crop (or its use), ERAs cannot be used to identify unanticipated effects resulting from unknown changes to the GM crop. The legislation requires unanticipated effects, which cannot be identified in the ERA, to be addressed in general surveillance (GS) plans. These are implemented once the GM crop is authorised for cultivation in the EU. We consider that farm questionnaires are particularly useful in this regard since they can monitor farmers' observations and track how the crop is being managed. Environmental surveillance networks are useful to track broader changes in agro-ecosystems but are of more limited value if used to analyse any impacts of introducing GM crops specifically.

Another concern for ACRE is that the narrow comparisons made in ERAs between a GM crop (and its use) and its non-GM equivalent are not placed in a wider context when adverse effects are assessed. Narrow comparisons may have little relevance to the actual environmental impact of introducing a GM crop into a farmed landscape. A greater focus on what constitutes an adverse effect would help identify additional comparisons and context required to generate a well-informed ERA. Please refer to Fig 2 on page 15 and Case Study D on page 16 for examples.

The legislation establishes that the ERA should characterise risks before and after taking risk management options into account. The Directive is not prescriptive about risk management options, including what scale they should operate at. This is helpful as it provides flexibility and opportunity for EU Member States to adopt measures that are compatible with their policies on sustainable agricultural production. ACRE considers that it is reasonable to manage small-scale risks to biodiversity and ecosystem functioning by requiring areas of land to be managed specifically for these purposes. However, in order to ensure that these measures are effective, the management options and relative areas need to be well-defined and supported by quantitative research.

ACRE recommends that ERAs of GM crops:

- *are based upon a more coherent understanding of environmental harm in its broader agro-ecological context;*
- *focus on clearly defined hypotheses of risk rather than on either hazard or environmental exposure;*
- *explore the most effective risk management options in cases where the GMO, or it use, poses a greater risk of harm to the environment compared to conventional crops/ agriculture.*
- *make better use of existing information. News of the first GM plant was published 30 years ago; a decade later the first GM crops were commercialised. Over this period, our understanding of plant genomes has increased significantly and a great deal of data on GM crops has been generated. ACRE considers it important to utilise this information when formulating ERAs in addition to wider information on agro-ecosystems. Additional data should be generated to support ERAs for specific GM crops within this context.*

Contents:

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1. ACRE

ACRE is an independent advisory committee composed of leading scientists and technical experts. Its main function is to provide statutory advice to UK ministers and ministers in the Devolved Administrations on the risks to human health and the environment from the release and marketing of genetically modified organisms (GMOs).

This report is one of three reports in which we consider the regulatory framework in which we operate, i.e. Directive 2001/18/EC. One report (Report 1: '*Towards an evidence-based regulatory system for GMOs'*) considers the limitations of the current regulatory framework and whether these can be addressed piecemeal or more effectively via an entirely new framework. Another (Report 2: '*Why a modern understanding of genomes indicates the need for a new regulatory system for GMOs'*) discusses the scientific validity of adopting the current approach to regulation, which is to control organisms based on how they were produced rather than on their novel characteristics. As the EU is unlikely to replace the current legislation in the near future, in this report we discuss how the environmental risk assessment (ERA) of GM crops could be implemented more effectively to support decision-making of GM crops intended for cultivation within the current regulatory framework.

2. Background to this report

EU legislation is intended to facilitate access to market of GMOs that are no more harmful to human health or the environment than their non-GM counterparts. To make this possible, decision makers require a clear understanding of the relative environmental risks associated with GMOs and their use and the risk management options that are available.

In 2008, the Council of the European Union adopted conclusions[2] that recommend improved implementation of the legislation for the deliberate release of GMOs into the environment. These include recommendations for 'strengthening ERA and monitoring arrangements'.

ACRE's experience over the last 5 years suggests that the interpretation of these recommendations can lead to a lack of perspective in the ERA and post-market environmental monitoring (PMEM) of GM crops. Our aim is to determine how strengthening the ERA can be interpreted in a way that promotes a more effective use of evidence when assessing the risks from GMOs.

To help us consider this issue, we held an evidence-gathering meeting[1] and invited experts to discuss aspects of ERA and PMEM.

3 The Current Legislation for Environmental Risk Assessment of GMOs

In order to understand the opportunities for more effective implementation of the current legislation, it is important to distinguish between what is required under GMO deliberate release legislation and how the legislation is interpreted.

Directive 2001/18/EC (which controls the deliberate release of GMOs) establishes that decisions on whether to authorise the release of GMOs should be based on a scientific, case by case assessment of the risk to human health and the environment. The term 'risk to human health' refers to risks that arise from environmental exposure; food safety is not part of this assessment.

Annex II of this Directive sets out a six step process for assessing the risks (Fig. 1). It is important to emphasise that Steps 2 and 3 are carried out in parallel (rather than in isolation) and Step 5 requires risk management measures to be taken into account before concluding on the overall risk. The legislation establishes that these risks should be characterised by comparing a GM crop and its use with that of its non-GM parental line(s)[2]. However, it does not preclude the use of additional, wider comparisons that allow statistically significant differences between a GMO and its non-GM counterpart to be placed in context. The legislation is not prescriptive about the nature of risk management options.

Annex II also sets out the issues that applicants must address in the ERA of higher plants (Appendix I). Annex III of the Directive establishes the information that applicants need to consider, such as parental organism, the genetic modification, characteristics of the GMO. The level of detail of information provided by the applicant will vary depending on the case. EFSA provides guidance on information requirements for the ERA of GM crops[3], but this guidance does not have legal status. These Annexes also provide the framework for gathering evidence on unintended effects, a term not used explicitly in the main body of the Directive.

[1] The agenda for ACRE's evidence-gathering meeting held on 21st March, 2013 and the associated presentations are available at: http://www.defra.gov.uk/acre/meetings/

[2] The Directive refers to a 'non-modified organism from which it is derived and its use under corresponding situations'.

[3] EFSA's GMO Panel guidance on the ERA of GM plants (2010): http://www.efsa.europa.eu/en/efsajournal/pub/1879.htm

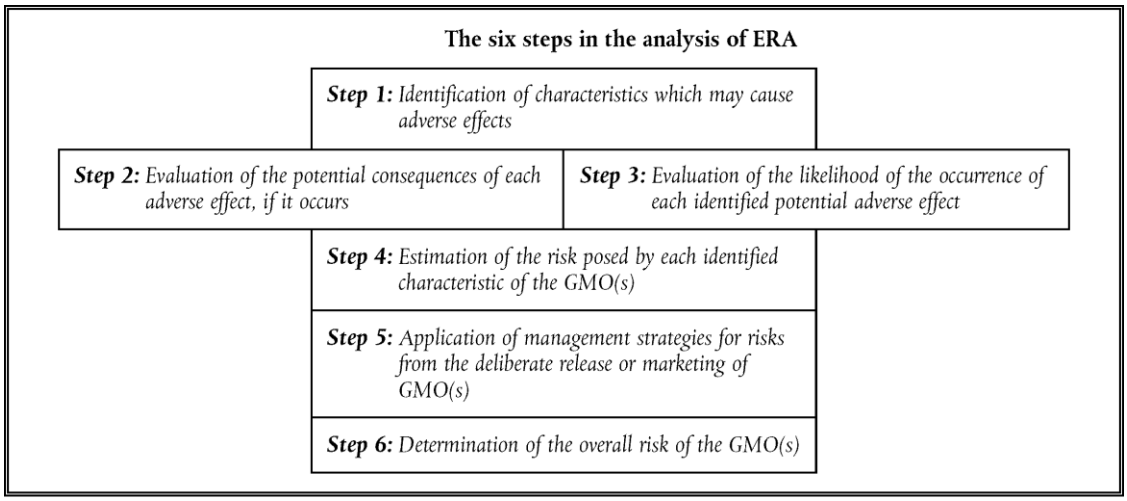

Fig 1: The six steps of Environmental Risk Assessment, according to Directive 2001/18/EC

The ERA of GMOs focuses on assessing hazard, likelihood and risk. The Directive defines hazard and risk (Box 1), but not adverse effect. Annex II of the Directive provides examples of 'potential adverse effects' and the mechanisms by which these may occur (Appendix II). In its ERA guidance for GM crops, EFSA cites the Environmental Liability Directive (ELD)[4]. This is helpful as it defines criteria for establishing whether environmental damage (adverse effect) has occurred, and conversely when a 'potential adverse effect' may not constitute an adverse effect/ harm[5] e.g. characteristics and conservation status of the species under consideration, magnitude of change compared to natural environmental fluctuations and the speed and capacity for recovery.

The GMO legislation does not use the term 'harm'. However, we refer to harm and adverse effect interchangeably in our advice and guidance documents. In our 2002 guidance on harm[6] we did not define harm but discussed the criteria we use to gauge it when considering applications to release GMOs into the environment. Ultimately harm is a consequence that society does not want in a given context. Whichever high-level working definition of harm regulators adopt, this will need to be resolved into which environmental parameters should be monitored to determine harm and what level of change is unacceptable. ACRE plans to consider this further next year; in particular how to extend the biodiversity and conservation focus of the ELD to an ecosystem services framework.

[4] Directive 2004/35/EC of the European Parliament and of the Council of 21 April 2004 on environmental liability with regard to the prevention and remedying of environmental damage

[5] A statistically significant change associated with a GM crop represents a potential adverse effect but does not necessarily constitute an adverse effect/ harm. This depends on wider factors, not all of which are scientific.

[6] http://webarchive.nationalarchives.gov.uk/20081107165902/http://www.defra.gov.uk/environment/acre/harm/pdf/acre_harm_report.pdf

Box 1. Key definitions

Adverse effect/ harm: significant damage to biodiversity or ecosystem functioning

Potential adverse effect: any negative impact on the environment (not necessarily harmful in the management of agro-ecosystems. The change may be regarded as acceptable).

Hazard[7]: (a harmful characteristic) is the potential of an organism to cause harm to or adverse effects on human health and/or the environment.

Risk[7]: the combination of the magnitude of the consequences of a *hazard*, if it occurs, and the *likelihood*[8] that the consequences occur i.e. risk of an adverse effect is a multiplicative function of hazard and likelihood.

Directive 2001/18/EC also sets out requirements for PMEM of GMOs. The legislation requires applicants to submit PMEM plans and it describes two types of PMEM[9]:

- Case-specific monitoring (CSM): to confirm that any assumption regarding the occurrence and impact of potential adverse effects of the GMO or its use in the ERA are correct;
- General Surveillance (GS): to identify the occurrence of adverse effects of the GMO or its use on human health or the environment which were not anticipated in the ERA.

CSM is therefore not required in all cases. By contrast, GS is required in all cases irrespective of the outcomes of the ERA. This is to identify and respond to any risks that had not been identified within the ERA. The legislation is not explicit in how GS should be implemented, except that 'cost effectiveness should be taken into account'[10].

4 Scope for more effective decision making through strengthening ERAs

Based on this understanding of the legislation, ACRE considers that there are areas where ERA implementation is inefficient

[7] As defined in Commission Decision 2002/623/EC.

[8] In its ERA guidance, EFSA refers to 'exposure' rather than 'likelihood' when referring to this element of the risk equation. Exposure to a hazard will be a major factor in determining whether the consequences of a hazard will be realised. In other scenarios, likelihood may be affected by other factors e.g. whether a farmer adopts particular agronomic practices when cultivating a GM crop.

[9] These concepts of CSM and GS are expanded on in Council Decision 2002/811/EC and in guidance from the European Food Safety Authority: http://www.efsa.europa.eu/en/efsajournal/pub/2316.htm.

[10] The principles of post-market environmental monitoring are described in Council Decision 2002/811/EC, which provides supplementary guidance to Annex VII of Directive 2001/18/EC.

4.1 Distinguishing between hazard and risk

The legislation sets out the steps for assessing risks to the environment, yet regulators often focus on hazard, regardless of the likelihood that the hazard will be realised. The result is that data are requested and included in ERAs that do not inform decisions on risk. This is confusing and adds to the regulatory burden without improving environmental protection.

In recent years there has been a debate within the EU on whether regulatory decisions should be based on a classification of hazards (i.e. on the intrinsic properties of products) or on an assessment of the risks. The main forum for this debate has been chemical regulation. A problem with a hazard-based approach is that the likelihood of an adverse effect occurring is not taken into account. This omission could lead to useful chemicals being prohibited even though they pose no actual risk or the risk could be managed. The GMO legislation, on the other hand, describes a framework that is designed to characterise risk and it is important that ERAs focus on the risk of adverse effects occurring rather than on hazards that are highly unlikely to translate into adverse effects under field conditions.

Some GMO ERAs focus on environmental exposure even when no hazard has been identified; for example, gene flow between plants is not an environmental risk *per se*, but it could pose a risk if there were a hazard associated with gene flow. This could happen if, for example, there was potential for a wild relative to become invasive in natural habitats after hybridising with the GM crop. The likelihood that this would occur and result in environmental harm should be assessed (Steps 2 and 3 in Fig 1). An example of where assessors and regulators have not focused on the risk is in dealing with an application to cultivate a GM potato (EH92-527-1). The applicant proposed monitoring for volunteer potatoes, and this was accepted by regulators, even though the ERA did not identify a risk (or hazard) associated with the occurrence of volunteers[11]. As no environmental risk hypotheses had been established, it was not clear what level of potato volunteers was unacceptable. In addition, the consent[12] stipulated 'field studies to monitor the potential adverse effects on potato-feeding organisms in the fields where *Solanum tuberosum* L. line EH92-527-1 is cultivated and in their vicinity'. This was despite EFSA's conclusion that 'no adverse effects on plant-associated organisms and soil function have been observed or would be likely from cultivation of the potato EH92-527-1'. A more recent example is described in Case Study A.

[11] In a notification (Reference C/SE/96/3501) from BASF to market a GM potato (*Solanum tuberosum* L. line EH92-527-1) with modified starch content.
[12] Commission Decision 2010/135/EC.

Case Study A: case-specific monitoring for persistence of Cry proteins in the soil

In its 2013 opinion on an application to cultivate 59122 maize, EFSA concluded that the binary insecticidal proteins expressed by this GMO (Cry34Ab1 and Cry35Ab1) were unlikely to pose a risk to non-target organisms[13] (NTOs). This included an assessment of soil organisms and micro-organisms. Thus, although there is a potential hazard, the actual risk was very small.

Having completed its assessment, EFSA then recommended that the applicant carry out post-authorisation monitoring ('case-specific') of binary protein levels in soils where 59122 maize is cultivated continuously. The reason given was that there was uncertainty about the persistence of these particular proteins in soils. There was no basis for deciding what should be measured and what the trigger point for intervention should be. Moreover, the evidence indicates very little uncertainty about persistence and that short-term persistence is not linked to harm[14].

ACRE concluded that as no environmental risk had been identified, there was no need for case-specific monitoring. If the EFSA recommendation were adopted, data would be generated at considerable cost for no purpose.

ERAs should address hazards and the likelihood that they will occur (under field conditions) in parallel. This is reflected in Figure 1. If there is no theoretical link between a characteristic of a GMO and greater environmental harm (compared with its non-GM counterparts) or if there is no likelihood of a hazard being realised (e.g. due to lack of exposure), no further evidence is required for the ERA or from PMEM.

Change is fundamental to agri-environments and within this context, GMO regulators need to understand if and under what circumstances a GM crop may pose a greater risk of environmental harm compared with conventional agriculture. It is also important that the management options available to minimise any risk are made apparent. Otherwise ERAs can lead to open-ended data gathering exercises, which may be scientifically interesting, but do not support decision-making (characterised as 'nice to know' versus 'need to know'). ERAs should address only those consequences that have the potential to result in environmental harm. There should be both a defined hypothesis of how adverse effects might arise from the GM crop and potential for these adverse effects to occur under field conditions. ERAs that confound hazard and risk of harm can lead to recommendations for management measures even though a risk has not been characterized.

[13] NTOs are organisms that are not the intended targets of the GM trait.

[14] Hopkins, D.W. and Gregorich, E.G. (2003) Detection and decay of the *Bt* endotoxin in soil from a field trial with genetically-modified maize. *European Journal of Soil Science* **54:** 793-800.

[15] Saxena, D. & Stotzky, G. 2001. Bacillus thuringiensis (Bt) toxin released from root exudates and biomass of Bt corn has no apparent effect on earthworms, nematodes, protozoa, bacteria, and fungi in soil. Soil Biology and Biochemistry, **33**: 1225–1230.

4.2 Linking cause and effect – testing plausible hypotheses

19. The legislation establishes that the risks of 'identified characteristics' of the GMO and its use that have the 'potential to cause adverse effects' should be assessed. ACRE is concerned that so-called 'generic hypotheses', which do not identify a causal link between a characteristic of a GMO (or its use) and harm, are the basis for some of the data requirements in GM crop ERAs. This approach leads to open-ended investigations because there is no credible scientific basis underpinning these hypotheses.

The legislation provides flexibility on data requirements and recently there has been a move to expect more data to address the potential for adverse effects to occur resulting from unknown, unintended changes to the GM plant (e.g. EFSA's 2010 scientific opinion on the assessment of potential impacts of GM plants on non-target organisms[15](NTOs); Case Study B).

It is not possible for ERAs to identify unintended effects by testing every characteristic of a GM crop and its use under every conceivable scenario (e.g. every species that may be exposed to the GM crop in different receiving environments across the EU). Therefore, it is important that ERAs adopt an approach that makes optimal use of existing evidence, including data gathered on the GM crop such as molecular, phenotypic and agronomic data. Where this 'weight of evidence' identifies unexpected changes to a GM crop, or its use, that can be linked to adverse effects, the ERA should follow a structured process to characterise the risk to the environment (Fig 1).

Case Study B: Data requirements for assessing potential unintended effects of GM crops on NTOs

In 2010, EFSA updated its guidance for ERAs of GM crops, giving more detail on how to assess potential unintended effects on NTOs. The guidance foresees that unintended effects may occur through changes in the GMO associated with the genetic modification (e.g. through inserting transgenes into the host genome) and through unanticipated effects associated with the trait. To address the former, EFSA recommended a weight of evidence approach taking into consideration molecular characterisation, phenotypic and agronomic data as well as compositional analysis. However, EFSA also requires applicants to carry out studies on a range of relevant NTO species using plant material just in case there is an unanticipated effect. This applies even if the introduced proteins/ metabolites have been proven to have no toxic properties and there is no evidence from molecular or comparative studies indicating that there is a hazard. In addition, to considering potential unanticipated toxic effects, EFSA recommends testing for sub-lethal effects on NTOs. These tests should include NTOs from different functional groups, including herbivores and pollinators.

[15] http://www.efsa.europa.eu/en/efsajournal/doc/1877.pdf

Applicants face a challenge in identifying ecologically relevant herbivores that are not also pests.

In an application to cultivate a GM herbicide-tolerant maize (GA21), pollinators were not present in sufficient numbers in a field study to enable a statistical analysis. In order to comply with EFSA's guidance, the applicant then conducted an acute toxicity study with honeybees to test for unintended effects on pollinators. This found no statistically significant effects on survival or feeding behaviour. As this study did not address unintended sub-lethal environmental effects, EFSA also requested a study that assessed honeybee larval development. EFSA was critical about some aspects of the information provided,[16] but concluded that there were no indications of unintended adverse effects on NTOs associated with GA21 maize.

After establishing that no unintended effects associated with the genetic modification *per se* are detectable, applicants are then required to consider whether the intended changes resulting from the genetic modification will have an adverse effect on NTOs. The current approach requires that NTOs representing several different functional groups are tested. This is the case, for example, with *Bt* plants, where guidelines for ERAs require tiered studies of the respective Cry toxins, even though their specificity and mode of action is well defined.

When a GM crop is modified to produce a novel protein or metabolite that is non-toxic at biological concentrations, ACRE considers that further NTO studies are not required to test for unanticipated adverse effects on NTOs unless there is a scientifically credible reason to do so i.e. a plausible risk hypotheses linking an altered characteristic of the GM crop to harm e.g. an unintended change in its composition or agronomic performance.

If tests with plant tissue demonstrate no adverse effects, ACRE's view is that there is no reason to repeat these tests using purified protein. It is more informative to use knowledge about the mode of action and specificity of the protein along with ecological and taxonomic knowledge of NTOs to frame the ERA (Fig. 1).

The regulation of GM stacked events is another example where ACRE considers the EU has moved from the principle of testing causal links between characteristics of a GMO and harm (Case Study C). 'Stacked events' refer to GMOs that have been generated by crossing existing GMOs to generate progeny containing multiple GM events.

[16] The applicant did not provide information on the size of the effect that the experiment was designed to detect and did not conduct a prospective power analysis (the latter is considered mandatory) but it did follow a standard protocol with slightly increased replication.

Case Study C: stacked events

The legislation does not require stacked events to be regulated when the individual events have been assessed separately and authorised. However, the EU has decided to take this approach and is developing evidence requirements for GMOs comprising stacked events[17]. This approach is not substantiated by our understanding of plant genomes or plant breeding. In general, crossing plants with desired traits does not pose a risk *per se*[18,19]. As such, ACRE's view is that there is no *a priori* reason to generate additional environmental data to assess the risk for stacked GM events when the individual events have been assessed independently. Collating data in the absence of a risk hypothesis is unproductive. It will also become increasingly impractical as the number of stacked events in individual GM crops increases[20]. The trend towards stacked traits will generate an increasing variety of segregants among the progeny. These will increase logarithmically as the number of transgenes increase (assuming these transgenes are unlinked). It is neither proportionate nor practicable to suggest that field trials should be conducted to assess this multiplicity of genotypes, simply on the assumed basis that there may be potential risks associated with unpredicted interactions between transgenes.

Exceptions may arise under particular circumstances. In these cases, risk hypotheses should be formulated and tested. Examples include where two traits when combined result in exposure of a wider range NTOs to the GMO than the individual traits do additively, or if they alter the toxicity of the GM crop through a synergistic mode of action. Such possibilities should be considered on a case by case basis and it would be the responsibility of the applicant to draft the revised ERA accordingly and present the relevant evidence to regulators.

ACRE considers that data on stacked GM events should not be required in addition to that provided for the individual GMOs unless there is a credible scientific reason for considering that the combination of the novel traits will alter the combined risk assessments of the individual GMOs.

ERAs should test plausible hypotheses linking a characteristic of a GM crop (or its use) to an adverse effect. A 'weight of evidence approach' is appropriate for identifying unintended changes to the characteristics of a GMO that can be linked to a defined adverse effect (e.g. a decline in honeybees). However, ERAs cannot be used to deal with unanticipated adverse effects. Instead, the legislation requires applicants to produce

[17] Commission Implementing Regulation on applications for authorisation of GM food and feed in accordance with Regulation (EC) no. 1829/2003 of the EU Parliament and of the Council and amending Regulations (EC) no. 64/2004 and (EC) no. 1981/2006. (in press).

[18] Weber N., Halpin C., Hannah L.C., Jez J.M., Kough J. and Parrott W.(2012). Editor's choice: crop genome plasticity and its relevance to food and feed safety of genetically engineered breeding stacks. Plant Physiology **160**: 1842 - 1853.

[19] Steiner HY., Halpin C., Jez J.M., Kough J., Parrott W., Underhill L. Weber N. and Hannah L.C. (2013) Editor's choice: Evaluating the potential adverse interactions within genetically engineered breeding stacks. Plant Physiology. **161**: 1587 – 1594.

[20] James C. (2012). Brief 44. Global Status of Commercialised Biotech/ GM Crops: (2012). International Service for the Acquisition of Agri-biotech Applications (ISAAA).

general surveillance plans to address the potential for unanticipated adverse effects to occur (please refer to section 4.5).

4.3 How should adverse effects be characterised?

The legislation establishes that ERAs should compare, under corresponding situations, characteristics of GM crops that have the potential to cause adverse effects with those of non-GM crops from which they are derived. Yet such data may have little relevance to the actual environmental impact of introducing a GM crop into a farmed landscape and as such, additional broader comparisons are necessary to provide this context. Greater clarity in defining adverse effects will help in identifying appropriate comparators and in improving ERAs.

The legislation requires the environmental impact of the GMO to be compared with its non-GM parental line(s). However, because there is no consensus on what constitutes adverse effect/ harm, it may be unclear what to measure, and on what scales.

In practice, adverse effects must be interpreted in terms of a measurable environmental attribute (defined as 'assessment endpoints' under a problem formulation approach[21]). The choice of environmental parameter is therefore central. Current ecological thinking suggests that harm should be considered at various levels, from individuals, populations, species, communities and ecosystem function. For example, impacts of organic farming on biodiversity in the UK are statistically significant in terms of species abundance, but not the functioning of trophic webs[22]. We consider that some measure of ecosystem function or value is appropriate in defining environmental harm, for example the metrics of the unsustainable use of natural capital that are under development[23]. Species-based comparisons are only appropriate if the species is of conservation concern and sensitive to changes in the cropped environment.

The choice of comparators is crucial. The legislation establishes that risk should be characterised based on comparisons between the GM crop and its non-GM parental line. However, this information in isolation is unlikely to inform decision-

[21] Wolt J.D., Keese P., Raybould A.F., Fitzpatrick J.W., Burachick M., Gray A.J., Schiemann J., Sears M., Wu F. (2010). Problem formulation in the environmental risk assessment of genetically modified plants. Transgenic Research 19: 425 -436.

[22] Macfadyen, S., Gibson, R., Polaszek, A., Morris, R.J., Craze, P.G., Planque, R., Symondson, W.O.C. & Memmott, J. (2009) Do differences in food web structure between organic and conventional farms affect the ecosystem service of pest control? Ecology Letters **12:** 229-238.

[23] First Report of the UK's Natural Capital Committee (2013). The state of our natural capital: towards a framework for measurement and valuation http://www.defra.gov.uk/naturalcapitalcommittee/files/State-of-Natural-Capital-Report-2013.pdf

makers on the risks associated with the cultivation of a GM crop. For example, a GM crop that has a significantly lower environmental profile than its non-GM comparator will be considered to pose a lower risk to the environment. However, if both the GM and non-GM variety of that crop have high impacts on farmland biodiversity relative to other crops, decision-makers should be aware that an increase in the cultivation of that crop due to the availability of GM varieties could result in a greater environmental impact. Therefore, it is important to set differences between a GM crop and its non-GM parental line in a wider agro-ecological context (Case Study D).

Ideally, comparators should be selected in ERAs that allow decision-makers to compare the environmental impacts of a GM crop with an externally derived limit or threshold, above which these limits are not regarded as being harmful (Fig 2).

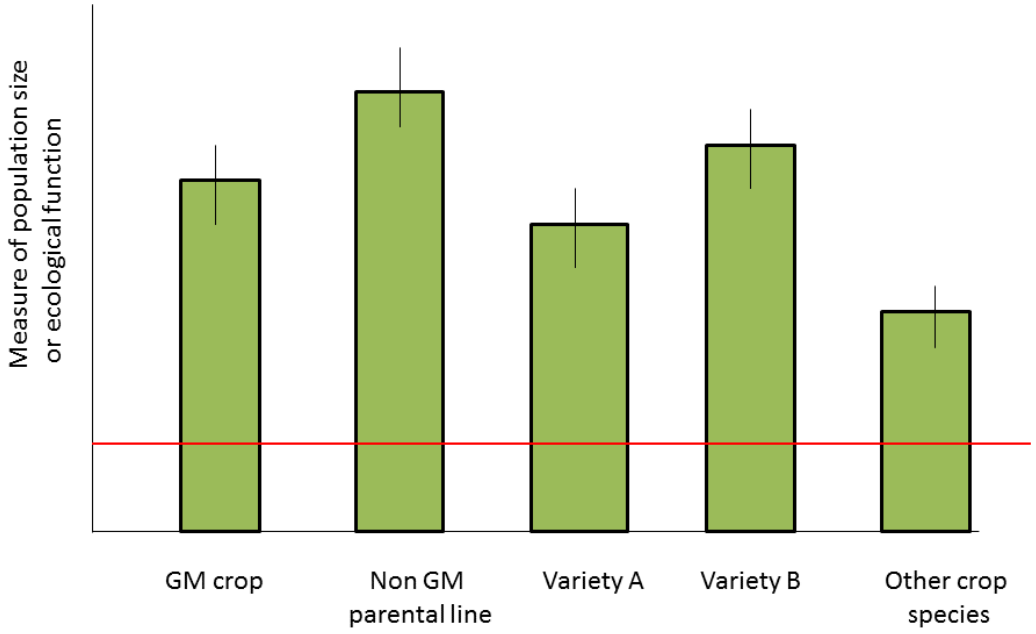

Fig 2. In this series of hypothetical comparisons of the environmental impact of GM and other crops, mean effects are shown by bars with standard error bars. The GM crop significantly underperforms compared with its non-GM parental line, but is within the range of variation shown by other varieties (A and B) of the same crop species, and also has a higher environmental performance than the other crop species grown by farmers on the same land. The red line indicates some externally-derived threshold, possibly based on the sustainable use of natural capital, below which the ecological measure should not be allowed to fall (adapted from Raybould's presentation to ACRE[1]).

The scale of the comparisons is also important. An ERA should not be sensitive to transient environmental changes, yet it remains extremely difficult to forecast whether a particular ecological change will become harmful in the longer term. This is because the farmed environment is strongly influenced by multiple drivers. One of these is agricultural practice, which changes over time in ways that cannot always be anticipated in the original risk assessment. Fortunately, it is often

possible to make judgements about which changes might increase risk without needing to make experimental comparisons of all combinations of management, soil and weather (Case Study D). Likewise, the environmental effects of any type of land management depend on the areas involved and their spatial configuration; a small ecological effect at small scales could be magnified if the GM crop were to be grown over a large proportion of the landscape. ACRE considers that ecological modelling will become increasingly valuable for guiding consideration of scale within ERAs. It is important to emphasise that these analyses should be founded on a plausible risk hypotheses linking a characteristic of a GM crop, or its use, to greater harm than conventional agriculture.

Case Study D: indirect effects of GM herbicide-tolerant maize on biodiversity

ACRE was asked to perform an ERA on an application to cultivate a GM herbicide tolerant (GMHT) maize in the EU.

A number of EU member states argue that the indirect effects of broad spectrum herbicides used in GMHT crops should be dealt with under specific plant protection products (PPP)[24] rather than GMO legislation. Other EU member states consider that these effects should be assessed but are unclear about what levels of weed control are acceptable in GMHT crops.

In the absence of wider policies to help frame this part of the ERA, ACRE focused on the nature and scale of changes that might constitute ecological harm.

The UK's Farm-scale Evaluations (FSE)[25] were an important source of evidence in this context. However, the FSEs were not designed to answer questions about acceptable levels of environmental harm *per se*. Instead they identified significant, ecologically relevant effects (i.e. potential adverse effects – see Fig 2) that reflected a propagation of herbicide effects on weeds to higher trophic levels.

In contrast to the other crops tested, weed abundance in GMHT maize was higher than in conventional maize. However, it is possible that these differences would change over time as farmers alter the way they use herbicides with non-GM and GM varieties of maize.

To place this uncertainty into context, it was important that ACRE considered the maize results alongside those of other crops in the trial (i.e. non-GM and GMHT beet and oilseed rape). This comparison demonstrated that both non-GM and

[24] The PPP legislation has been amended since ACRE carried out its initial assessment. It now includes a regulation on the sustainable use of pesticides which, in theory, should inform the GMO ERA. In addition there are on-going national and international discussions (e.g. reform of the EU's Common Agricultural Policy) about the management of land for food production and other environmental services.

[25] M. S. Heard *et al*., (2003) Weeds in fields with contrasting conventional and genetically modified herbicide-tolerant crops. 1. Effects on abundance and diversity *Phil. Trans. R. Soc. Lond. B*. 358, 1819.

GMHT maize supports little biodiversity and that a greater risk would result if the availability of a GMHT maize variety increased the area of maize that was grown.

This example demonstrates that in the absence of a political agreement on what constitutes an adverse effect in terms of weed control in maize fields, it is possible to provide decision-makers with an assessment that places the risk, including the associated uncertainty into some context using wider evidence and appropriate comparators. Nevertheless, we consider it important that decision-makers reach a greater consensus on what constitutes harm through considering broader agri-environmental policies on sustainable intensification.

Ideally, the experimental design and choice of parameters measured in ERAs should combine scientific knowledge and value judgements about the importance of different constituents of ecosystems and the services they deliver. Such decisions should be aligned with wider policy on the sustainable intensification of agriculture. ERAs should still be carried out on a case by case basis, structured around risk hypotheses linking characteristics of GM crops with harm. In the shorter term, in the absence of a consensus on what constitutes harm, we recommend that ERAs focus on known (and biological meaningful) magnitudes of effects that are detectable with a given power. The biological relevance should be determined relative to the impacts of a range of appropriate comparators e.g. as shown in Fig. 2.

ACRE considers that the legislation is currently interpreted in ways that seek statistically significant differences between GM and non-GM parental lines at a plot scale. Instead, ERAs should seek to assess biologically and societally significant changes to the agro-ecosystem as a result of introducing the GM crop according to the weight of evidence, including prior knowledge. Such a change in emphasis will greatly enhance the value of the ERA for environmental protection, whilst avoiding the costly collection of irrelevant data. ACRE recommends that in the short term, ERAs focus on biologically relevant effects that are detectable with a given power.

4.4 Managing risk and benefits

The legislation establishes that the ERA should characterise risks before and after taking risk management options into account. The Directive is not prescriptive about risk management options, including the scale at which they operate. ACRE considers that this flexibility is helpful and should be used optimally by decision-makers. However, risk management should not be implemented simply because there is no consensus on what type and degree of change, over what scale constitutes an adverse effect. This is likely to lead to conditions of consent directed at minimising potential impacts (hazards) rather than harm. This is not consistent with the principles of the legislation.

Whether the cultivation of a GM crop is likely to harm the environment to a greater extent than its non-GM counterparts is likely to be biased because current ERAs preclude an integrated view of environmental impacts. This is because the legislation does not provide for risk/benefit analyses[26]. We have considered the issue of addressing benefits in Report 1, in which we consider future changes to the regulatory framework for GMOs. Even so, the current legislation does not prevent decision-makers from placing any risks or significant uncertainties into context.

The legislation focuses on identifying and managing environmental risks associated with GM crops that are greater than those associated with non-GM crops. It is not prescriptive on the approach to risk management. Therefore, decision-makers have the option of adopting a landscape view, in which food production is concentrated in some areas (e.g. field centres), and biodiversity is the focus in others (e.g. at field margins, or in nearby areas of land). This may be more productive in optimising the delivery of both crops and biodiversity compared to managing a landscape in which they are expected to co-mingle[27]. A negative environmental impact of a GM crop at a small scale which is currently perceived as an environmental risk could be mitigated by differently managing other areas of land. Such spatial segregation may be a way of managing the risk of biodiversity decline associated with GMHT crops, through so-called biodiversity offsetting. For example, it has been estimated that leaving 2 % of a GMHT beet crop unsprayed can mitigate the effects of reduced numbers of weeds on the rest of the field[28].

ACRE considers that it is reasonable to manage small-scale risks associated with GM crops by requiring areas of land to be managed for biodiversity and ecosystem functioning, as long as the management options and relative areas are well defined and supported by quantitative research. PMEM can then focus on the presence of these managed areas, rather than on costly biodiversity monitoring exercises. ACRE considers that such offsetting is most practical at the farm scale, but does not rule out larger scale land management from ERAs in principle.

[26] This is based on: (1) the stated objective of the ERA as set out in the legislation (please refer to paragraph 8), (2) the examples of adverse effects provided in the legislation do not include risks associated with not adopting a technology and (3) the information requirements that are set out in Annex 3, which underpin the ERA in general do not facilitate a risk/ benefit analysis

[27] Hodgson, J.A., Kunin, W.E., Thomas, C.D., Benton, T.G. & Gabriel, D. (2010) Comparing organic farming and land sparing: optimizing yield and butterfly populations at a landscape scale. Ecology Letters **13** 1358-1367.

[28] The number was arrived at using data from the Farm Scale Evaluation of GMHT Beet. Pidgeon, J. D., May, M. J., Perry, J. N. & Poppy, G. M. 2007. Mitigation of indirect environmental effects of GM crops. *Proceedings of the Royal Society B-Biological Sciences,* 274**,** 1475-1479.

5. Post-market environmental monitoring

The 2008 EU Council conclusions place importance on 'strengthening monitoring arrangements'. As case-specific monitoring is linked to the ERA, our conclusions on the optimal implementation of ERAs are relevant to case-specific monitoring. This means that case-specific monitoring should address hypotheses linking a characteristic of the GM crop with an adverse effect rather than carrying out monitoring that will not affect decisions on whether a GM crop should continue to be cultivated in the EU or whether conditions of consent should be added or removed (please refer to Case Study A).

The requirement for applications to set out GS plans to identify unanticipated effects that could not be predicted in the ERA, poses a greater challenge because there are no risk hypotheses to test. This invites open-ended data gathering exercises that may provide information about environmental change, but that provide little insight into the environmental risks associated with planting the GM crop. As ACRE observed in a recent report, this can add greatly to the regulatory burden without enhancing environmental protection[29].

Any strengthening of GS monitoring arrangements would most effectively focus on GS that is closely associated with the GM crop. Two of the tools that the legislation suggests may be helpful in GS are farm questionnaires and existing environmental surveillance networks (ESNs). Farm questionnaires could cover the performance and management of the GM crop and selected farm-scale data whereas data collected from ESNs could be analysed to detect change in the farmed environment. However the power of the latter to detect small changes within a few years is low. Multiple drivers influence change in agro-ecosystems, so any change detected could not be unequivocally linked to the GM crop, and would require further experimental work and data analysis. The strength of ESNs is as an alert system for change more broadly, rather than as specific surveillance for GM crops.

Seeking evidence of unanticipated effects can become an open-ended quest for information, which can be expensive and unhelpful to decision-makers. Farm questionnaires that monitor farmers' observations and track how the crop is being managed are appropriate tools for the general surveillance of GM crops. The collation and analysis of data from environmental surveillance networks could be valuable as part of a broader system that tracks changes in agro-ecosystems (i.e. it is not specific to monitoring GM crops).

6. Conclusions

[29] ACRE's report on the Post-market Environmental Monitoring of GM crops (2013) is available at: http://www.defra.gov.uk/acre/sub-groups/env-monitoring/

In Reports 1 and 2, we conclude that the framework for controlling GMOs in the EU is out-dated and not fit for purpose. Regulatory frameworks need to evolve along with the evidence, especially when dealing with novel technology. This includes the EU's legislation for controlling GMOs. ACRE's recommendation is that the current framework should be replaced by a system that regulates organisms based on the novelty of their characteristics rather than on how they are produced. It should also take benefits, as well as risks, into account to allow for more informed decision-making.

ACRE appreciates that even if there were an appetite for a new regulatory system for dealing with novel organisms in the EU, this would take a number of years to adopt. Consequently, it is important that the EU operates the current system optimally. Whereas ACRE agrees that implementation of the GMO legislation needs improvement, we do not agree that the solution is generically to increase data requirements, which is the direction the EU appears to be heading.

ACRE's view is that ERAs (and PMEM requirements) will be improved if the EU is more strategic in how it uses evidence. In particular, we recommend the EU to:

- *develop a more coherent understanding of what constitutes an adverse environmental effect/ harm in a broader agro-ecological context;*

  There is currently a tendency to focus on statistically significant differences rather than on environmentally significant adverse effects/ harm. There are several components to addressing this issue, which involve a much clearer shared understanding of what constitutes harm; more flexibility over the appropriate comparators and better appreciation of the importance of spatial and temporal scales when compiling ERAs. Applicants need to know the standards they need to fulfil in order to provide the relevant evidence in ERAs;

- *focus on clearly defined hypotheses of risk rather than on either hazard or environmental exposure;*

  This would counter the tendency to collect data not relevant to risk assessment and management. It will also counter the EU's increasing tendency to pursue the possibility of unintended effects without having a plausible risk hypothesis to test. ACRE recommends using a weight of evidence approach to identify characteristics of a GM crop (or it use) that could be linked to harm. This approach is consistent with Annexes II and III of Directive 2001/18/EC.

- *seek options for environmental risk management as integral components of ERAs;*

There is increasing understanding of how to manage environmental risks on farmland. This knowledge could be used to develop ERAs that incorporate evidence-based risk management. However, conditions stipulating risk management measures in consents to cultivate GM crops will need to be flexible to allow for differences in EU receiving environments, national policies and uncertainties about levels of adoption and cultivation practices by farmers.

- *make better use of existing information.*

  There is a tendency for the EU to establish information requirements before considering the information that is already available. Structuring ERAs around what is already known (including what is considered harmful) and then identifying evidence gaps on a case by case basis will result in more reliable assessments. The adoption of a 'problem formulation' approach[21] will help to structure assessments and establish what evidence is required and why.

Appendix I: Issues that applications for the cultivation of GM higher plants should address (taken from Directive 2001/18/EC).

1. Likelihood of the GMO to become persistent and invasive in natural habitats under the conditions of the proposed release(s).
2. Any selective advantage or disadvantage conferred to the GMO and the likelihood of this becoming realised under the conditions of the proposed release(s).
3. Potential for gene transfer to other species under conditions of the proposed release of the GMO and any selective advantage or disadvantage conferred to those species.
4. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO and target organisms (if applicable).
5. Potential immediate and/or delayed environmental impact of the direct and indirect interactions between the GMO with non-target organisms, including impact on population levels of competitors, prey, hosts, symbionts, predators, parasites and pathogens.
6. Possible immediate and/or delayed effects on human health resulting from potential direct and indirect interactions of the GMO and persons working with, coming into contact with or in the vicinity of the GMO release(s).
7. Possible immediate and/or delayed effects on animal health and consequences for the feed/food chain resulting from consumption of the GMO and any product derived from it, if it is intended to be used as animal feed.
8. Possible immediate and/or delayed effects on biogeochemical processes resulting from potential direct and indirect interactions of the GMO and target and non-target organisms in the vicinity of the GMO release(s).
9. Possible immediate and/or delayed, direct and indirect environmental impacts of the specific techniques used for the management of the GMO where these are different from those used for non-GMOs.

These are the issues that must be addressed if the ERA is for the deliberate release of a GM higher plant. The issues are virtually the same for non-plant GMOs. Applicants use the evidence that they have submitted in responding to the questions listed in Annex III of the Directive to address these issues.

Appendix II – taken from Directive 2001/18/EC

Potential adverse effects of GMOs will vary from case to case, and may include:

- disease to humans including allergenic or toxic effects;
- disease to animals and plants including toxic, and where appropriate, allergenic effects;
- effects on the dynamics of populations of species in the receiving environment and the genetic diversity of each of these populations;
- altered susceptibility to pathogens facilitating the dissemination of infectious diseases and/or creating new reservoirs or vectors;
- compromising prophylactic or therapeutic medical, veterinary, or plant protection treatments, for example by transfer of genes conferring resistance to antibiotics used in human or veterinary medicine;
- effects on biogeochemistry(biogeochemical cycles), particularly carbon and nitrogen recycling through changes in soil decomposition of organic material.

Adverse effects may occur directly or indirectly through mechanisms which may include:

- the spread of the GMO(s) in the environment;
- the transfer of the inserted genetic material to other organisms, or the same organism whether genetically modified or not;
- phenotypic and genetic instability,
- interactions with other organisms,
- changes in management, including, where applicable, in agricultural practices.