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New Plant Breeding Techniques

New breeding techniques have developed rapidly in recent years, allowing plant breeders to introduce new, or modify existing, traits efficiently in key crops. There is debate over whether some of these techniques constitute genetic modification (GM) as defined in EU Directive 2001/18 and are thus subject to the various EU GM regulations. This note outlines some of the new techniques, their applications and the regulatory challenges they raise.

Overview

- The term New Breeding Techniques (NBTs) covers a range of methods that could accelerate improvement of crop varieties.
- NBTs include emerging techniques commonly referred to as 'genome editing' (POSTnote 541) that aim to manipulate DNA at specific locations to rapidly generate potentially useful traits.
- There is debate over how these techniques should be regulated, and whether some or all of them fall within the scope of EU legislation on genetically modified organisms (GMOs).
- Some of the crops produced using these techniques are difficult to distinguish from conventionally bred (non-GMO) plants.
- Following the vote to leave the EU, the UK may choose to make its own regulatory decisions regarding NBTs.

Background

Agriculture faces major production challenges at a time of increasing pressure from population growth and climate change. One way of increasing future yields is to develop crop varieties that can make better use of limited resources. Plant breeding aims to either take advantage of existing genetic variation or to generate variation from which desirable traits can be selected. A range of new breeding techniques (NBTs, Box 1) have been developed that can be used to modify the genetic make-up of a plant variety in a targeted way in order to introduce new traits or modify existing ones. Of the techniques outlined in Box 1, those collectively referred to as genome editing have been most widely adopted by researchers. CRISPR-Cas9 shows particular potential for crop development because of its relatively low cost and ease of use.

Researchers have already used NBTs to produce crop varieties (Box 2) that would have been difficult to obtain through traditional breeding methods. Such methods could reduce the time and effort required to develop crops with desirable traits, but may also raise new challenges for regulators. For example, in some cases the resulting plants may be virtually indistinguishable from their conventionally bred counterparts The UK is a global centre of excellence

Box 1. New Breeding Techniques (NBTs)

New Breeding Techniques (Box 1) typically involve making targeted changes to a plant's DNA in order to modify the plants physical characteristics (traits). The changes made can vary in scale from altering a single base (DNA is made up of four bases, A, C, G and T, the letters of the genetic code) to adding or deleting one or more genes (a DNA sequence containing the recipe for making one or more proteins). The most widely used NBTs include:[2]

- Genome editing to modify DNA at one or more specific sites selected by the researcher. The three main techniques (CRISPR-Cas9, Zinc Finger Nucleases and TALENs) each use an enzyme (a nuclease) to cut the DNA at a specific location. Researchers are able to exploit the mechanisms that repair these cuts to make edits to the DNA (see POSTnote 541).
- A specialised form of genome editing called Oligonucleotide-directed mutagenesis (ODM). ODM allows the introduction of targeted changes (mutations) to one or just a few bases of DNA.
- Cisgenesis (transferring a gene from the same or a closely related species) and intragenesis (inserting a reorganised regulatory coding region of a gene from the same species).
- Using epigenetic processes to change the activity of genes without changing the DNA sequence.

for plant science. However, plant breeders and the biotechnology industry fear that the uncertainty surrounding the regulation of these techniques acts as a constraint to innovation.[1] This POSTnote outlines the new techniques, looks at their potential applications and concerns about their use, and explores the options for regulating them.

Breeding Techniques

Conventional breeding

Conventional breeding has been used for millennia to manipulate plants for agriculture by exploiting natural variation, initially without understanding the underlying genetics. However, recent advances in plant genetics have allowed the development of marker-assisted selection, which links the genes associated with desirable traits to specific markers on the genome, thus allowing rapid and accurate selection for those traits. For more than 60 years, plant breeders have also been able to increase the range of natural variation available by exposing seeds to chemicals or radiation (mutagenesis), to introduce new variants. Such approaches have resulted in significant improvements for thousands of varieties in traits such as yield, crop quality and disease resistance.

Genetic modification (GM)

In the 1980s, advances in biotechnology allowed researchers to add desirable traits to crops by inserting genes from other species into random locations in the plant's genome. This technique, known as transgenesis, is one form of genetic modification (GM) that allows certain traits to be introduced into crops rapidly. The transfer of these traits would not have been possible through conventional breeding, but requires knowledge of the genes conferring the trait in question. While many traits have been the subject of GM approaches, the two that have been most widely commercialised are insect resistance and herbicide tolerance. Both of these traits have the potential to help reduce agricultural loss.

New breeding techniques (NBTs)

New breeding techniques have created additional options to conventional breeding and transgenic technology. Collectively NBTs allow researchers to insert or remove whole genes, make small changes to the DNA, or change the activity of genes without modifying their sequence (see Box 2 for examples). They give researchers more precise tools for increasing variation in specific genes. For example, inserting a whole gene at a specified location is similar to established GM approaches but can reduce problems associated with random insertion.[3] Deleting (or silencing) a gene can remove an undesirable trait more rapidly than conventional breeding. Similarly, replacing a DNA sequence with a different one could allow the swapping of different versions of the same gene more quickly and precisely. While the products of some NBTs may make use of a transgenic GM step early in the process, they can result in plants containing no foreign DNA that are not readily distinguishable from conventionally bred plants.[4]

A number of traits currently targeted by conventional breeding and GM technologies could potentially be achieved more efficiently using NBTs. NBTs may also allow the development of crops with a wider range of traits and potential applications. Traits under consideration include:[9]

- disease resistance,
- drought tolerance,
- improved nutritional quality,
- improved shelf-life,
- reduced allergenicity (the potential to cause an allergic reaction).

Lack of knowledge about the genetic basis for many of the more desirable plant traits is a key factor limiting the application of NBT (and GM) approaches. However, the rapid adoption of genome editing is indicative of the potential of NBTs for generating new plant varieties as knowledge of plant genetics improves.

Box 2. Examples of Current Applications of NBTs

Herbicide-Tolerant Oilseed Rape (Canola)

The first commercial product resulting from an NBT was developed by Cibus, a US-based company. It used a technique called oligonucleotide directed mutagenesis (ODM) to generate a variety of canola that is tolerant to sulfonylurea herbicides. Using ODM, Cibus was able to introduce a single base mutation, which occurs naturally in related species. Cibus claims that mutations introduced by ODM are indistinguishable from those arising naturally. However, NGOs such as Genewatch and EcoNexus argue that ODM could potentially give rise to additional, unintended, changes.[5]

In 2014, this crop became the first NBT-derived product to gain market approval in the US and Canada and has been cultivated in the US since 2015. Cibus has approached national regulatory bodies within the EU to determine whether plants developed using ODM fall under the GMO regulations. An analysis commissioned by several German agricultural and environmental associations concluded that products of ODM do fall within the EU GMO legislation. However, regulatory bodies in six EU member states have considered ODM and concluded that it is a form of mutagenesis that can be excluded from this legislation.[6,7] The European Commission has yet to rule on the issue.

Late Blight Resistant Potatoes

A UK research programme from The Sainsbury Laboratory has developed potatoes that are resistant to the disease late blight. Researchers inserted genes for blight resistance from a wild relative of the potato into commercial potato varieties using cisgenesis, an NBT using similar transformation techniques to transgenesis and thus currently regulated under EU GMO legislation.[2]

Waxy Corn

The first genome edited crop produced using CRISPR-cas9 is a corn variety developed by US company DuPont Pioneer. Genome editing was used to inactivate a gene leading to corn with a high amylopectin starch content. This is milled for a number of everyday consumer food and non-food uses, including processed foods and adhesives. In April 2016, the US Department of Agriculture decided not to regulate this variety because it does not contain any introduced foreign material.[8]

Potential Concerns with NBTs

NGOs are among those who have expressed general concerns that the patentable nature of crops developed using NBTs may lead to the food production chain being controlled by a small number of multinational agrochemical companies which own seed patents (POSTnote 517). They have also suggested that there is a risk of some genome editing techniques having unintended effects, such as editing DNA at sites other than those intended - so-called "off-target" effects.[5] However, the frequency of these effects has not been fully determined for many techniques and their effects on the final plant are unclear at present.[10] Finally, some NGOs are concerned about the potential cumulative effects of using NBTs to make multiple small changes to the same plant variety.[11]

Several scientific bodies have conducted reviews of the evidence relating to the potential risks of GM crops. The Royal Society[12], UK Council for Science and Technology[13] and the European Academies Science Advisory Council (EASAC)[14] have all concluded that GM crops present no greater risk to humans, or the environment, than conventionally bred crops. Many researchers argue that genome editing techniques offer greater precision than either current GM or mutagenesis methods and therefore may pose fewer risks.[15] EASAC has also published a statement on NBTs noting their potential value and "the lack of any new safety issues emerging".[16]

Current EU Regulation

All new varieties of crop seed are regulated in the EU through a registration process requiring a minimum of two years' field testing designed to provide assurance of uniqueness, stability, quality and improved performance.[17] There is considerable debate over whether all or some of the NBTs fall within the scope of EU legislation on GM organisms (see below).

EU GMO Regulation

In the EU, GMOS are regulated under the Deliberate Release Directive (2001/18/EC). The EU approach is often described as process-orientated because it is the process of genetic modification that triggers regulation. The Directive defines a GMO as an "organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination". Crops produced by exposing plants to chemicals or radiation to induce mutations are explicitly exempt from the scope of GMO legislation, on the basis that these methods have a long history of safe use. Applications to market GMOs in the EU undergo risk assessment by the European Food Safety Authority (EFSA) before Member States vote on whether to grant authorisation for release of the GMO into the environment. The assessment considers potential safety factors of both the trait and the final product, such as whether the plants are toxic, likely to cause allergies or likely to transfer novel genes to other organisms.[18]

While a number of GM products have passed the risk assessment procedure, only one GM crop currently has EU approval for commercial cultivation (granted in 1998). This has led many researchers and industry representatives to argue that the current EU regime is not working.[9,13,19] Criticisms include delays in the assessment procedure, the inefficiency of the approval process[13] and that the potential benefits of the new varieties are not taken into account. The high EU regulatory costs for new crop varieties classified as GMOs may also be a barrier to innovation, particularly for medium-sized enterprises and public sector researchers with limited resources.[20]

EU Regulation of NBTs

In 2007, the European Commission established a working group to consider the regulatory status of NBTs. It identified eight main technologies, of which the four outlined in Box 1 have been most widely adopted by researchers. EASAC has suggested that new techniques should be exempt from GMO legislation when the resultant product is free from genes foreign to that species, or when the end product is very similar to plants generated using conventional breeding techniques. This view is shared by many researchers.[16,21] However a number of environmental NGOs, scientists and lawyers disagree. Some NGOs published a joint position paper setting out a case for classifying all products of NBTs as GMOs,[11] arguing that this was necessary on safety grounds and to allow consumer choice.

The European Commission's working group on NBTs has considered whether such techniques fall within the scope of EU GMO legislation. The final report was produced in 2012, but never officially published. The draft report suggested that intragenesis and cisgenesis (Box 1) should fall under Directive 2001/18/EC. Its recommendations on the regulatory status of the other techniques have not been published[2] and the Commission has twice delayed the announcement of its final legal analysis. It also has not given a timeline for publishing its opinion prompting accusations of regulatory paralysis from industry and research institutions. The French Council of State has since elevated the issue to the European Court of Justice[22] which is expected to produce a final and binding opinion on the interpretation of EU GMO law by 2018/19. However, subsequent legal challenges in relation to specific NBT applications may delay the process further.

Future UK Regulatory Options

In 2014, 61% of UK agricultural products exports went to EU countries.[23] While care is needed not to jeopardise this trade, the UK's decision to leave the EU raises the possibility of the UK adopting a different approach to regulating NBTs than that adopted elsewhere in the EU. Three options have been widely discussed in the debate on regulating NBTs.[24]

- adopting a product-based approach to regulation where each new crop is assessed on the basis of the novel trait(s) introduced,
- maintaining the current process-triggered approach and regulating all NBTs as GMOs,
- a mixture of product- and process-based regulation.

Product-based Approach

The first of these options is the approach adopted by North American regulators (Box 3). It involves regulating new plant varieties based on the trait(s) introduced instead of the method used to generate it. This is the approach favoured by bodies such as EASAC[14], the BBSRC[3] and the House of

Box 3. Regulation of NBTs in North America
Canada
In Canada, all new plant products are assessed for their safety and environmental impact under the same trait-based system irrespective of the technique used to develop them. Any plant with a novel trait must undergo a full risk assessment. Unlike the approach adopted by the EU, this framework is adaptable because the regulatory trigger remains consistent as breeding techniques continue to evolve[9]. Over 190 products have been approved through this system since 1993, many of which are produced using NBTs.[25]

USA
In the USA, the main regulatory approach is a product-based risk assessment. Where new products are generally recognised as safe because they are similar to existing food they do not require separate pre-market approval. Discussions are currently under way on how to adapt the current regulatory system to meet the challenges raised by NBTs. In 2016, several crops developed using NBTs were deregulated including varieties of apples and mushrooms which resist browning and a drought resistant corn variety (Box 2).

Commons Science and Technology Select Committee[9] which suggested that the risk posed by a new crop variety "has little to do with how it is made and is mostly to do with the characteristics it displays and how it is used in the field". Any such move in this direction would potentially make trade between the UK and North America easier, but would put the UK at variance with the EU regulatory system. A purely product-based approach would regulate all novel products, even if they were produced using previously accepted techniques such as mutagenesis.

Process-triggered Approach
Environmental and consumer NGOs argue against the introduction of a product-based regulatory system on the grounds that it offers consumers less protection from potential risks to human health or to the environment. Some NGOs suggest that information about the process helps to alert the risk assessors to unanticipated changes and effects.[26] They also suggest that consumers have the right to know how a product has been made so that they can, for instance, choose to avoid products labelled as containing GMOs. Such groups favour the second option of retaining the current EU process-triggered system based on the precautionary principle.[27] While such a system may make trade with the EU easier - depending on the nature of trade deals negotiated with the EU - it lacks adaptability as new techniques are developed.

Product- and Process- Based Approaches
The final option is a mix of product- and process-based regulation. Some researchers suggest that given public concern over GMOs (Box 4), the absence of data on public attitudes to NBTs and the unknown nature of the potential risks associated with NBTs; this type of approach might represent the most reasonable compromise. A light-touch regulatory approach incorporating a risk assessment based on the NBT used to ensure that only desired changes have been made, could protect consumers without causing unnecessary oversight. One possible approach would be to regulate the product depending on whether the genetic changes could have been produced using conventional breeding. Under such a system, regulations would not apply to the herbicide-tolerant canola or to the late blight-resistant potatoes (Box 2) because in both cases the changes could have occurred naturally by random mutation (canola) or through breeding with a wild relative (potato). This option addresses some of the concerns posed by NGOs. However, some researchers argue that the extent of DNA modification is not a good way of classifying the actual risks posed by NBTs.[24]

Box 4. Public Attitudes Towards GMOs
A survey conducted by the Food Standards Agency in May 2016 found that 23% of respondents reported concerns about GM foods. Research for the European Commission in 2010 suggests that the UK public are among the least opposed to GM foods in Europe[28]. For example, 44% of those polled in the UK agreed that GM foods "should be encouraged" compared with just 10% of those polled in Greece and Cyprus. Those who oppose GM foods are generally concerned with how natural or interventionist the DNA modification is; it is unclear whether the increased precision associated with NBTs might alleviate these concerns. While companies such as Bayer have commissioned some initial research,[29] there is little information available about public attitudes towards genome editing and other NBTs. Market acceptance of NBT products may be influenced by the success of therapeutic applications of these techniques in humans (POSTnote 541). Public perceptions of potential consumer-facing benefits such as improved health and nutrition may also prove to be an important factor.

Endnotes

1. Jones HD, *Are plants engineered with CRISPR technology GMOs?*, Biochemist, June 2016
2. *New Techniques Working Group Final Report*, European Commission, 2012
3. *New Techniques for Genetic Crop Improvement*, BBSRC, 2014
4. *New techniques used in plant breeding*, ACRE, 2014
5. *Genetic Engineering in Plants and the New Breeding Techniques*, EcoNexus, 2015
6. Position statement of the ZKBS on new plant breeding techniques, BVL, 2012
7. *Advice on a plant breeding technique involving oligo-directed mutagenesis: RTDS*, ACRE, 2011
8. *Confirmation of Regulatory Status of Waxy Corn Developed by CRISPR-Cas Technology*, USDA, 2016
9. House of Commons S&T Select Committee report, 5th Report, 2014-15
10. Zhang et al, *Molecular Therapy - Nucleic Acids*, 4, 11, 2015
11. *New techniques of genetic engineering*, NGO Joint position statement, 2016
12. *GM plants: Questions and answers*, Royal Society, 2016
13. *GM Science update*, CST, 2014
14. *Planting the Future*, EASAC, 2013
15. Ricroch et al, *Editing EU legislation to fit plant genome editing*, *EMBO, 2016*
16. *New Breeding Techniques*, EASAC, 2015
17. *Harnessing the opportunities of NBTs*, APPG Agscience AGM, 2016
18. *Making the food and farming industry more competitive whilst protecting the environment*, Defra, 2015
19. *NBTs - what are NBTs and why do they matter?* NFU, 2016
20. *NBTs. State-of-the-art and prospects for commercial development*, JRC, 2011
21. Regulatory approaches to modern plant breeding, ESA, 2015
22. www.gmwatch.org/news/latest-news/17257-european-court-of-justice-will-rule-whether-new-gmo-techniques-fall-under-gmo-law
23. Implications of a UK exit from the EU for British agriculture, NFU, 2016
24. Editing EU legislation to fit plant genome editing, EMBO, 2016
25. Health Canada – approved products, accessed 14 November 2016
26. *Application of the EU and Cartagena definitions of a GMO*, Greenpeace 2015
27. (COM (2000) 1) on the precautionary principle, updated Dec 2016
28. *Europeans and Biotechnology*, European Commission, 2010
29. www.populus.co.uk/wp-content/uploads/2016/11/OmCrop_Science_Website-2.pdf

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