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New techniques of genetic engineering

Why EU GMO law must be fully applied to the so-called 'New Plant Breeding Techniques'

The European Commission is considering whether genetically modified organisms (GMOs) that have been produced through a range of new techniques should be excluded from the European Union's GMO regulations. Biotechnology companies want to apply these techniques to engineer plants and animals for use in industrial food, biomass and biofuel production. They argue that these new methods to directly modify the genetic make-up of living organisms fall outside the scope of EU GMO regulations. This would mean that there is no risk assessment, labelling and monitoring of GM organisms produced by the new techniques and their derived products. The Commission has announced that it will present a legal analysis on the matter by the end of March 2016.

The new GMOs present a real risk to the environment and human health. Legal analysis shows that they are covered by EU GMO law. If they were to escape EU regulations, any potential negative effects on food, feed or environmental safety would go unchecked. European consumers, farmers and breeders would have no way to avoid GMOs.

The Commission should leave no doubt that all products of genetic engineering are subject to EU GMO law which requires rigorous risk assessment, detectability and labelling.

1 Which techniques are we talking about?

The biotechnology industry and the European Commission use the term 'New Plant Breeding Techniques' to refer to a diverse set of genetic engineering techniques:

- Gene-editing techniques including zinc finger nucleases (ZFN), TALENs, CRISPR/Cas, meganucleases and oligonucleotide-directed mutagenesis (ODM)
- Cisgenesis and intragenesis
- RNA-dependent DNA methylation (RdDM)
- Agro-infiltration
- Reverse breeding
- Grafting on a GMO rootstock

The biotechnology companies are claiming that all these techniques are "non-GM" and advertising them as "an effective alternative in light of the *de facto* moratorium on GMOs in Europe".[i] This is based on a very narrow definition of GMOs as being organisms that carry genes from unrelated species ('foreign DNA' or 'transgenes'), which is not in line with the EU regulations. The intention of this interpretation is to avoid regulation as GMOs.[ii]

Many of the techniques can be used in combination with each other, or several times over, in order to achieve the intended effect. Gene-editing, cisgenesis and intragenesis can be applied to both plants and animals, including farm animals, insects and fish for open release into the environment. Gene-editing may also be used to create 'gene drive' mechanisms with the aim to spread traits such as disease resistance into wild populations of plants or animals. Gene-editing in humans, which is not covered by the EU GMO regulations, is also possible and the subject of much debate.

An overview of the intended genetic modification and possible applications of each technique is given in the Annex.

EU GMO law

The basic laws governing GMOs are Directive 2001/18, Regulation 1829/2003 and Regulation 1830/2003. These laws do not prohibit the release into the environment of GMOs, or products derived from GMOs. Instead, they require risk assessment, detectability and labelling. Whether or not an organism is regulated as a GMO is determined by Directive 2001/18.

The stated aim of the EU GMO regulations is to "*protect human health and the environment*" (Directive 2001/18) and a "*high level of protection of human life and health, animal health and welfare, environment and consumer interests*" (Regulation 1829/2003). Recital 8 of Directive 2001/18 reads: "*The precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it*."

More than 60 GM crops have been authorised for import, and one GM crop (BASF's Amflora potato) also for cultivation, since the current framework came into force. (The authorisation was later annulled.) The only GM crop currently allowed for cultivation, Monsanto's MON810 maize, was authorised in 1998 under previous rules. No GM animal has ever been authorised for either cultivation or import into the EU.

2 EU GMO law applies

2.1 EU definition of a genetically modified organism

EU Directive 2001/18 defines a "*genetically modified organism*" on the basis of the process by which it has been created. According to the law, it is an "*organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*" (Article 2.2).

This definition makes sense because it is the process of genetic engineering that invariably leads to both intended and unintended outcomes, including also unpredictable changes to the DNA and its functioning, which may compromise the final product's health and environmental safety.

The EU Directive lists a number of processes as resulting in GMOs falling under the EU definition. However, this list is explicitly open-ended ('inter alia') so that the Directive can be applied to technical developments in genetic engineering. One example of a GM process is the insertion of genetic material (e.g. stretches of nucleic acid such as RNA or DNA) prepared outside the organism

('in vitro') into a host organism, which causes an alteration of the organism's own genetic make-up (Annex IA, Part 1).

Importantly, it is only the characteristics of the process, not the characteristics of the resulting organism, that determines whether or not an organism is a GMO. It is irrelevant whether the intended genetic alteration could, in theory, also arise from mutations that are induced by chemicals or radiation, or that occur spontaneously. It is also irrelevant whether the inserted genetic material originates from a crossable species, or whether it is present in the final product.

Those who wish to classify the new GMOs as products of traditional breeding are well aware of the Directive's focus on the process rather than product of genetic modification. It is one of the main reasons why they are calling for a different regulatory approach.

2.1 Exemptions

The Directive mentions two processes of genetic modification whose products are exempt from the scope of the law. These are mutagenesis and cell fusion between crossable organisms. However, these processes are only exempt "*on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms*" (Annex 1B). This means that organisms whose genetic material has been altered using RNA or DNA sequences prepared outside the cell, or using GMOs, cannot be exempt from the law.

The exemptions are presented as a closed list. They must be interpreted narrowly, in line with the precautionary principle.[iii] They encompass "*certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record*" (Recital 17).[iv] None of the new techniques can claim to have such a "*long safety record".*

2.3 Organisms derived from GMOs

The Directive also applies to organisms that are derived from GMOs. This includes organisms produced through grafting on a GM rootstock, reverse breeding and some types of RdDM. The functioning of these organisms could be impeded by compounds and metabolites of the GMO, giving rise to safety implications.

3 Safety risks warrant rigorous case-by-case testing

There are risks and uncertainties associated with each of the new GM techniques, some of which are common to all.[v] Given that many of the techniques are new, it is not yet possible to fully evaluate the potential for adverse effects.[vi] The fact that they can be used in combination and multiple times means that these effects can be significant even when individual use may be low risk. As yet, there has been no or little assessment of the biosafety implications of combining the techniques.

Gene-editing, for example, is poorly understood, especially in plants. As little is known about its mode of action it is also difficult to identify potential hazards.[vii] We know, for example, that gene-editing can alter the DNA in additional places to those intended (off-target effects) but the factors that determine the frequency and type of these changes are largely unclear.[viii] Gene-editing to create so-called 'gene drive' mechanisms could have irreversible effects on whole ecosystems.[ix]

The developers of gene-editing techniques such as CRISPR-Cas9 or ZFN have strongly warned against their application in human reproductive cells.[x] They highlighted that "*research is needed to understand and manage risks*" of CRISPR-Cas9 specifically, including "*the possibility of off-target alterations, as well as on-target events that have unintended consequences*."[xi] The biotechnology

companies seem to have no such qualms when it comes to the technique's application in plants or farm animals, which are regulated by EU GMO laws.

It would be irresponsible therefore to allow the new GMOs onto the market without prior risk assessment.

Cibus' SU Canola

The US company Cibus has engineered an oilseed rape that tolerates spraying with sulfonylurea (SU) herbicides, using a technique known as oligonucleotide-directed mutagenesis (ODM). This 'SU Canola' is now grown in the US. In 2014, it covered around 3 percent of total US oilseed rape acreage. Cibus has approached national authorities in at least six EU countries asking for confirmation that its product is not a GMO and can be released in field trials.[xii] In June 2015, however, the Commission asked all national authorities "*to await, as much as possible, the outcome of the Commission legal interpretation before authorising a deliberate release of organisms obtained with new plant breeding techniques*".[xiii] Cibus, meanwhile, expressed optimism that the Commission's decision "*will allow for the commercialisation of crop plants developed by ODM to occur in a timely manner*".[xiv]

4 Consumers, farmers and breeders need to know

A majority of Europeans is opposed to GM food. Research carried out in 2010 has found "declining support across many of the EU Member States – on average opponents outnumber supporters by three to one, and in no country is there a majority of supporters".[xv] (The Commission did not repeat this EU-wide research.) GM-free food labelling schemes are catching on quickly, boosting demand for non-GM ingredients and certification of non-GM products.

For these reasons alone, many farmers and breeders wish to avoid using GMOs, and to avoid their products being contaminated with GMOs. This is an important issue for the rapidly expanding organic sector in particular.[xvi]

5 Patents, not GMO regulations, put a break on breeding

Biotechnology companies are claiming that the new GMOs are needed to meet the upcoming challenges of plentiful and sustainable agricultural production. The same arguments are being used to promote other (transgenic) GMOs.

However, a drawback of genetic engineering is that it does not deal well with complex traits governed by many genes at once. So far, its commercial record is limited to two simple traits, herbicide tolerance and insecticide production, which have been introduced individually or in combination.[xvii] By contrast, traditional breeding techniques allow breeders to endow plants with complex traits such as disease resistance or drought tolerance.

All new GMOs are or will be patented. However, without GMO labelling, most breeders would not be able to distinguish them from non-patented plants. This could lead to considerable uncertainty for breeders and farmers as to what they can cultivate, breed or transform. It would slow progress in plant breeding and undermine the right of farmers to select and use their own seeds.

6 The way forward

Organisms derived from the new GM techniques should be regulated like any other GMOs. They should be subject to EU GMO authorisation, which requires

- comprehensive case-by-case risk assessment;
- methods for detecting, identifying, and quantifying the GMO that are publicly available in an EU database;
- documentation to track the GMOs and GMO products at all stages of the supply chain;
- consumer labelling of GMO products;
- post-market monitoring;
- GMO location register.

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Techniques under review by the European Commission

Technique	Intended genetic modification	Possible applications
Gene-editing techniques including zinc finger nucleases (ZFN), TALENs, CRISPR/Cas, meganucleases and oligonucleotide-directed mutagenesis (ODM)	"Re-write" parts of the genome by deleting, substituting or adding DNA sequences in pre-defined locations	e.g. herbicide tolerant oilseed rape, male sterile trees, hornless cattle, double-muscled pigs, disease-resistant 'gene drive' mosquitoes
Cisgenesis and intragenesis	Insert DNA sequences derived from the same or a crossable species	e.g. disease resistant apple, potato
RNA-dependent DNA methylation (RdDM)	Silence specific genes in a way that will usually disappear after several generations	e.g. delayed tomato ripening, insecticide production in potatoes
Agro-infiltration	Deliver genetic material to a plant transiently, for a maximum of one generation	e.g. vaccine, antibody production; research in model plants
Reverse breeding	Silence genes in charge of genetic recombination in the sexual reproduction process (as one step in the overall process)	creation of hybrids in e.g. maize, fruit trees
Grafting	Combine a non-GMO scion with a GMO rootstock (or vice versa)	e.g. disease resistant fruit trees