Briefing on the European Court of Justice ruling on genetically modified crops produced via mutagenesis

SUMMARY

On July 25th the European Court of Justice (ECJ) will make a ruling on whether a specific induced mutation process, used in the genetic engineering of plants, should be included within – or excluded from – the scope of current European legislation on genetically engineered plants.

The case, which began as an action brought about by several French NGOs to challenge French law on mutagenesis, was referred to the European Court of Justice in 2016 and has moved from being a 'local' issue to one of Europe-wide interest with both direct and indirect implications for the regulation of genetically modified crops and foods within the EU.

Beyond GM has prepared answers to some basic questions about the ECJ case, its background and its implications. What follows is (use internal document hyperlinks for ease of access):

More general information on the new genetic engineering techniques can be found on our website.

CONTEXT

The European Court of Justice (ECJ) case on mutagenesis must be seen in the context of the bigger picture of the genetic engineering of crops and foods, the evolution of the newer technologies used (sometimes called GMO 2.0) and how these are regulated in the EU.

European regulations are not perfect but for several decades they have provided a broad safety net which has largely prevented inadequately tested genetically modified crops and foods from being grown or entering the human food chain in Europe.

The current comprehensive regulatory framework governing the marketing of GMOs in the EU consists of various directives and regulations, including the following main building blocks:

- Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC ('the GMO Directive');
- Regulation 1829/2003 of 22 September 2003 on genetically modified food and feed; and
- Regulation 1830/2003 of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified organisms.

The purpose of these regulations is to "avoid adverse effects on human health and on the environment", in accordance with the Precautionary Principle (Article 191, Treaty on the Functioning of the European Union).

Directive 2001/18/EC contains what is known as a "mutagenesis exemption" which is directly relevant to the ECJ case.

THE CHALLENGES OF GMO 2.0

The tools and techniques that biotechnology companies use to genetically engineer plants are evolving. New genetic engineering techniques such as CRISPR-Cas9, TALEN, gene drives and synthetic biology are increasingly being used to genetically engineer food crops and foods. While the processes are scientifically sophisticated the results are still unpredictable and the products of these techniques remain largely untested and difficult to regulate.

Several new technologies are currently in play.

Some technologies like CRISPR-Cas9 are so 'easy' to use that they have become popular with 'biohackers' – lay people who want to experiment with the genomes of plants and animals. Biohacking is completely unpoliced and unregulated and while many fear that these unregulated experiments could lead to environmental or human harm, it is clear that even when used by trained scientists tools like CRISPR can have unintended or 'off-target' effects within an organism's genome.

The science of genetic engineering seems to be evolving faster than most regulators can cope with. This is good for biotechnology companies which want to get their technology out into a wider and more profitable market unhindered by the red tape of regulation; but is bad for everything else since it rides rough-shod over existing regulations, ignores the Precautionary Principle and presents risk to both the public and the environment.

In addition to using their considerable lobbying power to push new technologies through the system faster than regulators can cope with, manufacturers of genetically engineered crops and foods are also now seeking to find ways around existing regulations. A good example of the latter is the increasing use of genetically modified processing aids such as genetically engineered bacteria, enzymes and algae which are being altered to perform tasks these organisms would not normally perform such as producing food additives such as oils, flavourings and probiotics. This process is known as synthetic biology, or Synbio.

Another example is the switch from 'transgenic' organisms (combining the DNA of unrelated species) to 'cisgenic' organisms (combining the DNA of related species) which genetic engineers claim is more 'natural' – a claim that disregards the fact that the act of 'cutting', 'editing' or 'erasing' (all these

'soft' descriptors are in common use) a part of DNA sequence in the first place, causes unpredictable effects separate and distinct from those intended by the insertion of new DNA.

A further example is the gene drive which spreads the genetically engineered trait through a population of organisms in the natural environment. Because it happens outdoors rather than in a laboratory, some biotechnologists claim this makes the process 'natural'. Again this claim disregards the potential for gene drives to wipe out entire species in the wild – a serious consideration which has caused its inventor, Kevin Esvelt, to lobby against its use.

All of these claims for the naturalness of new genetically engineered or genetically modified organisms (GMOs) contradict the legal definition of a GMO, agreed by the World Health Organization, the United Nations and by every regulatory agency in the world: a GMO is an organism – plant, animal or micro-organism – whose DNA has been altered in a way that cannot happen in nature and/or which makes it function differently than it would in nature.

All genetic engineering techniques – new and old – alter the organism's genome in this way and this definition is important because naturally occurring foods are generally excluded from the patent landscape. Without this distinction biotech companies cannot patent their processes and their products – and patenting is the way that biotechnology companies make their money. This means that while the biotech company PR playbook may claim that GMOs are just an extension of a natural process, the law says otherwise.

WHAT THE CASE IS NOT ABOUT

The ECJ case is not about the safety or otherwise of genetically engineered crops and foods. Its narrow focus on mutagenesis means that it does not have direct implications for ongoing discussions about other forms of genetic engineering which are also currently the subject of much debate such as CRISPR-Cas9, TALEN, gene drives and various forms of synthetic biology.

However, it should be noted that the case is, in part, being seen by biotechnology corporations as a springboard for changes in the law on genetically engineered crops and foods – and could be seen as testing the ground for other legal challenges to the regulatory status of other types of genetic engineering processes used in farming and food production.

WHAT THE CASE IS ABOUT

In December 2014, nine French NGOs initiated legal proceedings over Article D.531-2 of the French Environmental Code, which is a part of the French law dealing with genetically modified organisms. In particular, they argued that herbicide tolerant varieties of rapeseed and sunflower resulting from new mutagenesis processes constitute 'new hidden GMOs' and that, as such, they must be regulated as GMOs under European law.

As part of the legal proceedings, on 3 October 2016, the French Conseil d'Etat referred four preliminary questions to the European Court of Justice (ECJ) for clarification on whether organisms resulting from new forms of mutagenesis should be subject to the GMO legislation.

These questions posed are:

- Are organisms obtained by mutagenesis, in particular new directed mutagenesis, GMOs?
- How Directive 2001/18/EC on GMOs and Directive 2002/53 on the common catalogue of varieties are working together, regarding the definition of GMOs and their respective field of application?

- In case all types of mutagenesis are excluded from the scope of Directive 2001/18/EC, could Member States implement their own regulation?
- Does Directive 2001/18/EC (GMOs definition, and its scope) comply with the Precautionary Principle regarding new genetic engineering techniques?

The case has been proceeding slowly but on 18 January 2018 the Court's principal advisor, the Advocate General, Michal Bobek, published his opinion.

The opinion was vague enough to allow both sides to claim 'victory'. Having noted that, in principle, mutagenesis is exempt from the requirements of the EU GMO Directive, the Bobek's opinion states that:

- Genetic material which has been altered in such a way that does not occur naturally can be characterised as a GMO.
- Mutagenesis which involves such material and/or the use of recombinant nucleic acid molecules would fall within the scope of the Directive.
- Where types of mutagenesis fall outside of the GMO Directive, individual member states can regulate separately provided overall EU law is respected.

The ECJ is not obliged to adopt the opinion of the Advocate General, however in practice it usually does. If it does it will then be up to the French Conseil d'Etat to make a ruling which may (or may not) declare that some, all or none of the new genetic engineering techniques fall under GMO law as it is applied in France.

For more on the possible fallout see Beyond GM's article *High stakes for CRISPR and GMO regulation in Europe*.

While these deliberations have been going on, the European Commission (EC) requested all member states to hold back on giving the all-clear on the use of crops and foods which result from the application of a suite of new genetic engineering techniques such as CRISPR-Cas9, TALEN and gene drives until the ECJ has published its opinion (which is due 25 July 2018). Indeed progress on regulating these techniques has been slow to non-existent since 2008.

WHAT IS THE MUTAGENESIS EXEMPTION?

In EU Directive 2001/18/EC genetically modified organisms obtained through mutagenesis are exempted, under certain conditions, from risk assessment and labelling obligations (among other obligations). As a consequence, these GMOs can generally be cultivated without having been subject to an environmental risk assessment and they can be marketed without traceability or labelling.

The exception was intended to be a pragmatic way of acknowledging the historical use of mutagenic techniques in plant breeding and the plant varieties that are on the market today as a result of them.

The coalition of French NGOs which brought the original case argue, however, that mutagenesis techniques have evolved since the adoption of the EU Directive in 2001 and are now at odds with exemption granted at that time. They further argue that plant material created by "modern mutagenesis" carries a risk of significant harm to the environment and to human and animal health and should be covered by the Precautionary Principle which is part of EU law.

WHAT IS MUTAGENESIS?

Mutagenesis is not one process but many. It has been around as an approach to plant breeding since the early 20th century. Using mutagenic substances (for instance, chemicals or radiation) on the

plant or on cells *in vitro* breeders have produced new varieties of plants with useful traits. Plants historically produced via this process include rice, maize, wheat, tomato, squash and soybean.

Plant breeders argue that they used these mutagenic techniques (often referred to as 'random mutagenesis') to change the whole plant, that they did not involve the insertion of any foreign DNA and that these strains were created so long ago that they have a proven history of safe use and consumption.

Biotech companies argue that they use the same techniques as historic plant breeders, but in a more 'precise' way to cause mutations on only a small part of the DNA. They refer to this as 'directed mutagenesis' or 'targeted mutagenesis'.

They further argue that this process results in fewer unintended mutations throughout the genome. However, this process is too new and too untested to make this claim categorically. What is more, because genes have multiple functions any direct damage to the genome is likely to result in multiple dysfunctions ('off target effects') elsewhere.

HOW DOES 'OLD' MUTAGENSIS DIFFER FROM 'NEW' MUTAGENESIS?

The claims of some scientists (and acquiescence to those claims in the media) give the impression that the precision of the new mutagenic process creates more predictable and controllable result. This has yet to be proven and there are no structures in place with which to test such claims.

The French case argues that new mutagenesis techniques are very different from older ones and are also untested and untried and therefore should not be covered by the mutagenesis exemption in Directive 2001/18/EC.

Mutations, whether they occur throughout the entire genome or at a single location in the genome are random events. They may or may not produce the desired result. They may also produce a range of unintended results. Current claims of precise mutation is not only an oxymoron, it also confuses – some would argue deliberately – process with outcome.

CAN MUTAGENESIS OCCUR NATURALLY?

'Mutations' do occasionally occur spontaneously in nature without any deliberate intervention by man. Often we do not know what causes them.

The example most often used by proponents of biotechnology is that UV radiation from the sun is a natural mutagen that has been significantly altering plants in the wild for years. There is no conclusive proof of this.

Plants require sunlight for photosynthesis and, as a consequence, are exposed to the ultraviolet (UV) radiation that is present in sunlight. While it is true that some frequencies of UV radiation are known mutagens, the most harmful of these are filtered out by the atmosphere. Thus all UV-C (< 280 nm, the most harmful of UV frequencies) and a significant part of UV-B (280-315 nm) are filtered out, while most UV-A radiation (315-400 nm) reaches the earth's surface.

If a dangerous sun was more or less constantly mutating our plants and crops we would see evidence of this everywhere. In addition, plants have evolved to produce substances that prevent damage from UV rays that do reach them – a good example of this are the antioxidant substances found in many plants which have been shown to protect the plant's DNA.

More importantly, studies of UV-induced mutagenesis involve laboratory experiments in which plants growing in normal sunlight are given 'supplemental' doses of UV-B or UV-C radiation well beyond anything they could be exposed to normally.

RNA - AN EXCEPTION TO THE EXEMPTION?

Although we are encouraged to believe that directed mutagenesis is 'new' it was already known in 2001, when Directive 2001/18/EC came into force. For this reason the directive also places another condition on products that might be covered by the exemption: that the mutagenesis technique must "not involve the use of recombinant nucleic acid molecules" (RNA). Directed mutagenesis is rarely used just on its own and many new techniques do use RNA (For more on the use of RNA alongside other new genetic engineering techniques see here).

Whether the mutagenesis technique involves the use of RNA is becoming the critical question for determining whether new mutagenesis techniques are exempt.

Unfortunately, the Advocate General's opinion did not address (nor was it asked to) the different molecular gene-editing techniques being used to create new crop and animal varieties. The Advocate General's opinion also did not define (nor was it asked to) "recombinant nucleic acid molecules," nor explain what it means for a mutagenic technique to "involve" those molecules.

This means that crucial questions that might help clarify matters such as…

- Does combining nucleotides to create the components of CRISPR-Cas9 complex result in a "recombinant nucleic acid molecule?"
- Does "recombining" mean the joining of any two pieces of DNA or RNA from the same species, or do they have to be from different species?
- Does "involve" mean that a "recombinant nucleic acid molecule" has been used at any step in the mutagenesis process, or only that the molecule is in the final product?

…are left unanswered.

If the ECJ final ruling also does not address these issues (and again it has not been asked to and therefore is unlikely to) then it will be left to EU regulators to determine the answers, possibly through future court cases.

In the vacuum left by this ruling it is likely we will see biotechnology corporations proposing to 'help' legislators make amendments to existing regulations – or create new regulations – to clarify matters. The nature of this 'help' would be to change the wording of regulations to reduce 'red tape' and make them more 'fair' to business.

NGOs, which are far less well-resourced and less able to influence policy, fear that such moves could lead to the destruction of the EU's GMO regulation which has for years ensured a rational approach to protecting citizens and the environment from the harms of unrestricted GMO crops and foods.

IS ANY OF THIS RELEVANT TO THE UK?

The UK has no coherent food and farming policy post-Brexit. Because of this it is likely that any approach to GMO regulation will be shambolic and piecemeal.

With no legislation in place the UK is likely, in the first instance, to take its cue from the EU. However it has been clear for some time that the Tory government is publicly and vociferously pro-

deregulation and pro-GMO. Indeed the government's view is that an emancipated agro-technology (including genetic engineering) industry is a key economic driver for the UK going forward.

Environment Secretary Michael Gove, for example, has suggested that that gene editing could be used to create "more valuable livestock". But, as if to illustrate the general chaos of the government's approach he has also made confused off-hand statements about whether GM crops would continue to be banned in the UK post Brexit.

The government's position completely ignores the views of UK citizens, the majority of whom still have legitimate questions and concerns about the widespread application of genetic engineering in farming and food.

What is more, unless Brexit results in significant changes in the disposition of devolved powers (as the government has been angling for on a "temporary basis") Scotland, Wales and Northern Ireland are free to take a different view on any recommendations or policy emerging from Westminster. The result could be chaos.

WHERE DO WE GO FROM HERE?

In many ways the law is the wrong vehicle to address these issues. In any legal case the scope of enquiry is naturally limited to a few key points. Thus, relying on legal interpretation to reshape EU regulations could result in lengthy and haphazard progress.

Even when legal process produces useful results, political pressure can see these buried by those with better lawyers, bigger budgets and more ingrained agendas. In 2016, for example, the European Commission put aside a legal opinion confirming that genetically modified organisms (GMOs) produced through gene-editing and other new techniques fall under EU GMO law.

The action followed pressure from the US government, the details of which were revealed by a series of internal Commission documents obtained by European NGOs under freedom of information rules, which showed intense lobbying by US representatives for the EU to disregard its GMO rules, which require safety testing and labelling. This action can be seen as part of a larger rolling process which is seeing the European countries crumble under US lobbying pressure and retreat from science-based regulation.

To truly make sense of the GMO issue requires a constant eye on the bigger picture of food and farming, not just as a key economic driver but as a foundation of a healthy and thriving society. It also requires that the issue of genetic engineering be put into context – as a symptom of a system that is largely broken but which refuses to reinvent itself.

To produce rational regulation requires a reframing of the debate beyond piecemeal legal and scientific arguments, because whilst the process of genetic engineering is a scientific process, and that process should (but doesn't always) inform our regulations, the issue itself, how it intersects with food, culture, environment and sustainability is not just science issue.

Widening the discussion to include environmental, economic, philosophical and human scale factors we might ask, for instance, how do genetically engineered crops and foods stack up against the multiple criteria for sustainability such as food quality and culture, social values, environment, health, economy and governance?

Such questions naturally broaden the scope of enquiry to include the Court of Public Opinion, and it is here and not the European Court of Justice or any other courts in the EU, where the ultimate fate of the new genetic engineering techniques is still most likely to be decided.