A comparison of the EU regulatory approach to directed mutagenesis with that of other jurisdictions, consequences for international trade and potential steps forward

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Brief heading: Discrepancies in the regulatory approach to the products of directed mutagenesis

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Summary

A special regulatory regime applies to products of recombinant nucleic acid modifications. A ruling from the European Court of Justice has interpreted this regulatory regime in a way that it also applies to emerging mutagenesis techniques. Elsewhere regulatory progress is also ongoing. In 2015, Argentina launched a regulatory framework, followed by Chile in 2017 and recently Brazil and Colombia. In March 2018, the USDA announced that it will not regulate genome-edited plants differently if they could have also been developed through traditional breeding. Canada has an altogether different approach with their Plants with Novel Traits regulations. Australia is currently reviewing its Gene Technology Act. This article illustrates the deviation of the EU's approach from the one of most of the other countries studied here. Whereas the EU does not implement a case-by-case approach, this approach is taken by several other jurisdictions. Also, the EU court ruling adheres to a process-based approach while most other countries have a stronger emphasis on the regulation of the resulting product. It is concluded that, unless a functioning identity preservation system for products of directed mutagenesis can be established, the deviation results in a risk of asynchronous approvals and disruptions in international trade.

Key words: directed mutagenesis, genome editing, precision breeding, GMO, CJEU

Introduction

Modern plant breeding exploits the progress in various scientific disciplines in order to increase the available genetic variation and to increase the precision with which the genetic material is managed. Genetic variation allows the development of crops with combinations of traits that are beneficial in one way or another. Randomly induced mutagenesis, using radiation or mutagenic chemicals, has for many decades enabled breeders to increase the genetic variation available for breeding and cherry-pick the rare beneficial mutations among the treated plant material (Ahloowalia & Maluszynski, 2001). Since the 1970s, recombinant nucleic acid technology provided breeders with access to the genetic material of basically any organism – a huge breakthrough in terms of available genetic variation. However, the potential of recombinant nucleic acid technology also prompted discussions around the biosafety of this very potent technology (Berg *et al.*, 1974) and the first regulatory frameworks were developed for these so-called genetically modified organisms (GMOs).

In recent years, genome editing techniques have also been developed that enable directed (or targeted) mutagenesis yielding beneficial mutations without the mutational load of randomly induced mutagenesis. These techniques for directed mutagenesis include (*inter alia*) site-directed nuclease systems such as clustered regularly interspaced short palindromic repeats (CRISPR) together with a Cas (CRISPR associated) endonuclease protein, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs), meganucleases and the nucleic acid-based oligonucleotide-directed mutagenesis (ODM). It is beyond the scope of this review to describe the genome editing techniques in detail or the various genetic alterations that these enable, however several recent reviews are available on various aspects, such as the technical details (NTWG 2012, Chen and Gao 2014, Abdallah et al. 2016, Hilscher et al 2017, HLG SAM 2017), specifically on CRISPR systems (Bortesi and Fischer 2015, Ding et al. 2016, Paul III and Qi 2016, Samanta et al. 2016, Stella and Montoya 2016, Arora and Narula 2017, Volpi e Silva and Patron 2017, Yin et al. 2017), applications in plants (Brinegar et al. 2017, Hilscher et al 2017, Ricroch et al. 2017, Zhang et al. 2017), as well as the historical development (Songstad et al. 2017) and comparisons with other breeding techniques (Georges and Ray 2017).

The current GMO legislation in the European Union (EU), centers around Directive 2001/18 (the release directive) and Regulations 1829/2003 and 1830/2003. One of their regulatory approaches consists of an pre-market authorization regime for GMOs, which are subject to an environmental and human health risk assessment. After authorization, GMOs are subject to traceability, labelling, monitoring and liability obligations. In Art. 2(2) of the release directive, a GMO is defined 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". As some precision breeding techniques mimic naturally occurring processes one could argue that these techniques would already not be considered GMOs according to this definition. However, Art. 3(1) in connection with Annex 1B of the EU release directive exempts 'mutagenesis' from the definition. According to some views, such an exemption would not have been needed if such techniques would not have been covered by the GMO definition in the first place (See Poortvliet et al, 2018, discussing the various options of the legal categorization). Mutagenesis is a technology that yields genetic alterations mimicking natural, spontaneous mutations, albeit through processes that are generally considered the result of human intervention. Hence, mutagenesis is considered a GM technique under EU law. For several years though, it was not clear what kind of mutagenesis techniques would be covered by the exemption. The reason for doubt was

especially the wording of recital 17, which states that "*(t)his Directive should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record.*" This wording gave rise to concern whether new mutagenesis techniques, particularly directed mutagenesis, would also be covered by the exemption. For a technical analysis of which genetic alterations fall under the mutagenesis exemption, we recommend Wasmer and Robienski (2018).

Whether precision breeding techniques, such as directed mutagenesis, are subject to the provision of the release directive has been subject to debate in the literature. (Eriksson, 2018; Hartung & Schiemann, 2014; Jansson, 2018; Krämer, 2015, Sprink *et al*., 2016; Spranger, 2015). Legal scholars have pointed out the fact that there is a difference between the legal requirements regarding the scope and the exemption in the release directive (Spranger, 2015). In particular, it was under question whether the mutagenesis exemption should be interpreted strictly in the sense given to the word *mutagenesis* at the time of adoption of the release directive in 2001 (Spranger, 2015) or whether it also covers mutagenesis techniques developed after 2001 (AG Bobek, 2018). Should Annex IB of the directive be interpreted in a historical way (i.e. what the lawmaker intended in the time of writing) or in an evolutionary way taking into account also developments since that time (i.e. what the lawmaker would have regulated in case it would have implemented the provisions today?). This resembles a methodological question in law, namely where to draw the line between interpretation (the responsibility of the Court) and law-making (the responsibility of policymakers) (Purnhagen & Rebasti, 2007).

In this article, we analyze a recent ruling from the Court of Justice of the European Union (CJEU) on mutagenesis and the scope of the release directive, and discuss its consequences. We compare the EU approach to directed mutagenesis, incl. the CJEU ruling, with the approach taken by several other jurisdictions and discuss the implications for international trade when there is discrepancy among the approaches. We also point to some potential steps forward for EU policy makers.

The EU court case on mutagenesis

A judgment from the Court of Justice of the European Union (CJEU) concerning the interpretation of Articles 2 and 3, and of Annexes 1A and 1B, of the release directive (CJEU, 2018) provides an indication to how EU will apply existing legislation to directed mutagenesis

under its current regime. The case was initiated when the French Conseil d´État (Council of State) on 3 October 2016 requested a preliminary ruling from CJEU following complaints from nine French organisations that the French government refused to ban the cultivation and marketing of herbicide-tolerant oilseed rape varieties obtained by randomly induced, or other types of, mutagenesis.

The CJEU Advocate General (AG) delivered first an Opinion on 18 January 2018 (AG Bobek, 2018). In this Opinion, the AG first highlighted that products derived from mutagenesis are in principal covered by the definition of a GMO (AG Bobek, 2018, paragraph 60). Otherwise one would not need to exempt mutagenesis from the definition (AG Bobek, 2018, paragraph 62). With regards to the interpretation of the exemption, the AG rejected the historical interpretation for the benefit of an evolutionary interpretation, which opens up the possibility to include directed mutagenesis techniques into the exemption via interpretation (AG Bobek, 2018, paragraph 110). To come to this conclusion, AG Bobek ironically uses an argument from historical interpretation: it is unlikely that the drafters of the directive did not account for potential technological process (AG Bobek, 2018, paragraph 77). In the eyes of the AG this solution does not result in the fact that directed mutagenesis techniques will remain unregulated. Rather, he invites the EU institutions or Member State policymakers to provide clearer and more detailed regulations within the existing general regulatory regimes for trade in goods, foods and seed law. If neither of the two picks up the ball, however, he sees potential tensions with the precautionary principle (AG Bobek, 2018, paragraph 122). Following the AG's solution, the majority of directed mutagenesis techniques are exempted from the release directive but can be regulated at the member state level. However, Member State or EU-wide initiated legislation will be under scrutiny of EU primary law, in particular the freedom of goods in Art. 34 TFEU. Even if member states or the European Commission (EC) do not initiate additional legislation, plants derived by mutagenesis would be regulated under the EU seed law. If national regulation would concern directed mutagenesis in foods and feed, in addition the EU legal regime regarding food and feed law would be applicable (Purnhagen *et al*., 2018a).

The CJEU delivered its judgment on 25 July 2018. Contrary to the AG, the Court followed a historical interpretation. Whereas it was confirmed that mutagenesis techniques are considered GMOs (CJEU, 2018, paragraph 30), and that these under certain conditions are excluded from the scope of the directive (CJEU, 2018, paragraph 37 and 40), the Court relied strictly on Recitals 4, 5 and (in particular) 17 of the release directive which states that the exemption is applicable to those GM techniques which have been conventionally used in a number of

applications and have a long safety record (CJEU, 2018, paragraph 45). Whereas the court also acknowledges that the release directive does not provide any definition of the techniques to be excluded (CJEU, 2018, paragraph 43), it is also taken into consideration that the case includes techniques of directed mutagenesis involving the use of genetic engineering which have been developed since the release directive was adopted in 2001 and for which the risks have not been established with certainty (CJEU, 2018, paragraph 47). This interpretation, which would subject the products of directed mutagenesis to the provisions of the release directive, thus implies that the two "subcategories" of randomly induced mutagenesis and directed mutagenesis are sufficiently distinct to warrant differential treatment under the release directive. The CJEU also does not take into account that many products of directed mutagenesis would be indistinguishable from those resulting from natural, spontaneous mutations (thus not altered in a way that does not occur naturally) (for the impact on the EU regulation of this lack of consideration, see Purnhagen *et al*., 2018b) and instead adopts a more process-based interpretation resulting in these products being classified as GMOs in the first place based on the use of recombinant nucleic acids in the process. In conclusion, this judgment (which cannot be appealed) indicates that the EU may subject the products of directed mutagenesis to the provisions of the release directive and the ones referring to it (Purnhagen *et al*., 2018a).

The approach to directed mutagenesis in other jurisdictions

It is important to see the EU approach to directed mutagenesis in an international context as other countries, particularly on the American continents, have already developed, or are in the process of developing, a regulatory procedure for handling the products of New Breeding Techniques (NBTs) including directed mutagenesis. We will here describe the approach taken by Argentina, Brazil, Chile and Colombia in South America, Canada and the United States in North America, and Australia, and then continue with a comparative analysis to the EU approach.

Argentina

Argentina was one of the first countries in Latin America to implement a system to evaluate the biosafety of GMOs for agriculture use. Argentina also recognized early the value of NBTs for crop R&D (Whelan & Lema, 2015). CONABIA decided to work with the definitions of GMO and of biotechnology contained in the Cartagena Protocol on Biosafety to the Convention on Biological Diversity (CBD), and include these in Resolution 701/11 that regulates activities

with GMOs for agricultural use. CONABIA applies different criteria to determine if a product derived from NBT should be considered GMO or not. The first consideration is that products obtained through any NBT must be submitted to a prior consultation. The second one is the scope of genetic change; a novel combination of genetic material is the insertion into the genome of genes or DNA sequences that are a part of a genetic construct. From these criteria and after two years of debate, Resolution 173/15 was adopted presenting a procedure to determine if a product obtained using NBTs is covered or not by Resolution 701/11. Specific features to highlight in this resolution are: 1) Its analysis is based on a case by case logic, 2) It is not restricted to a list of NBTs, 3) If the product is still at the design stage, the developer can consult the committee about the status of the hypothetical product, and 4) The Biosafety Committee must perform the assessment within 60 days. This procedure is outlined in Figure 1 and described hereafter. During the early consultation procedure, the Biosafety Committee analyses if there is a new combination of genetic material in the genome. In affirmative cases, the product is considered a GMO and the applicant is notified that the product will be subject to the corresponding regulatory procedures. In negative cases, the committee analyses if the development of the NBT product uses a transgene temporally. If it does, and the final product is not free of transgene, it is considered a GM. If the product does not contain a new combination of genetic material in the genome generated by the use of these techniques, the applicant will be notified that the product does not fall under the GMO Resolution and the plants will be treated as conventionally bred varieties. In order to initiate the consultation, the information that the applicants shall submit is the following: 1) the breeding methodology used to obtain and select the crop, 2) the new trait or characteristic introduced, 3) the evidence of the genetic changes present in the final product, 4) the phenotypic characterization, and 5) the evidence of removal of the temporary transgene used to obtain the product (if applicable). The Biotechnology Directorate and CONABIA may request the applicants to file additional data and information in order to complete their assessments. A similar procedure applies to hypothetical products. Only a few cases have hitherto been presented for consultation. These include annual crops as well as ornamental plants and fruit trees. The main traits are herbicide resistance, high oleic acid content and modifications for consumers and industries. Some of the cases presented to the commission were non-browning potatoes with an edited polyphenol oxidase gene, developed by INTA (http://intainforma.inta.gov.ar/?p=42900), and herbicide-tolerant soybean developed by the company Bioheuris. Three cases of genome-edited animals have also been presented (https://www.lanacion.com.ar/2150187-una-firma-de-rosario-desarrolla-cultivos-resistentes-a-herbicidas-con-edicion-genica).

Australia

Australia is operating under the regulatory framework legislated in 2001, referred to as The Gene Technology Act 2001. This Act provides a working framework for research, field trials and commercial release of GMOs. In parallel, Food Standards Australia New Zealand (FSANZ) assesses applications for approval for food derived from GMOs. Currently, nearly all cotton grown in Australia is GM and in 2017 there was 491,528 hectares of GM canola. In addition to the national legislation that provides this working framework the State and Territory Governments have the ability to restrict the release of GMOs. As a consequence, while most states permit the commercial cultivation of approved GMOs some do not. The Gene Technology Regulator initiated a review of the Act to provide clarity about whether organisms developed with new technologies are subject to regulation as genetically modified organisms (GMOs) and to ensure that they are regulated in a manner commensurate with risk. Submissions were sought late 2017 to early 2018 from the public and stakeholders on proposed amendments, with the issues raised in the submissions being currently under consideration. The next step will be for proposed amendments to be provided to the Commonwealth and State and Territory governments. Any amendments would need to be legislated by the Parliament. The key proposals covered a range of regulatory frameworks with "option 3" being viewed as best supporting the effectiveness of the legislative framework at this time. For this option organisms modified using site-directed nucleases without templates to guide genome repair (i.e. SDN-1) would not be regulated as GMOs. Currently, if a template is used to guide genome repair (i.e. SDN-2 and SDN-3), the resulting organisms are GMOs, as are organisms modified using oligonucleotide-directed mutagenesis. This is argued to be based on an assessment of risk, compliance enforceability and consideration of the policy settings of the regulatory scheme. With respect to RNAi the proposal is that applying RNAs to temporarily induce RNAi are techniques that are not gene technology providing there are no changes to genomic sequences. A further consideration for the uptake of new breeding technologies in Australia will be the decisions of its major export partners, as the majority of its major crops, such as wheat, are exported. For example, even if Australia does not regulate a specific new breeding technology but its major markets for the resulting agricultural product do, that would have substantive consequences that need to be assessed by the relevant industry and stakeholders.

Brazil

The current Biosafety Law in Brazil was adopted in 2005 (CTNBio, 2005). The law gives the mandate to the Brazilian National Biosafety Technical Commission (CTNBio) to evaluate how

new technologies might impact biosafety for the environment and human/animal health in Brazil and then, if necessary, to propose legislation regarding these new technologies. When the law was created, most of the NBTs were at its infancy, so they were not really considered at that time. Thus, in 2014 the CTNBio created a working group of experts that studied these new breeding techniques such as gene editing for three years, aiming to propose a more updated normative. The CTNBio´s Normative Resolution Nº16 (RN16), published on January 15th 2018, under the scope of the Brazilian Biosafety Law, was approved by unanimous vote among CTNBio´s 27 members (CTNBio, 2018). The normative, which is also based on other countries' experiences, evaluates in a case-by-case consultation system if a product generated by the NBTs will be considered a conventional or a transgenic organism. Under the RN16 consultation procedure developers provide information on the product, including the methods used to generate it. The absence of recombinant DNA/RNA in the progeny, the presence of genetic elements that could be obtained by conventional breeding; the presence of induced mutations that could also be obtained by older techniques, such as radiation or chemical mutagenesis, or even the presence of induced mutations that could occur naturally, are in a case-by-case analysis considered conventional organisms/products in many situations. In June 2018 the CTNBio evaluated, under the scope of RN16, the first genome edited organism in Brazil submitted to analysis. A *Saccharomyces cerevisiae* strain received mutations present in four genes from another *S. cerevisiae* strain by the use of a CRISPR/Cas9 strategy where only the mutations remain present in the final product. The genome edited organism, developed to improve alcohol production from sugarcane, was considered a conventional yeast since these mutations could be obtained by classical breeding or other older mutagenesis induction techniques, but with much less precision. A genome-edited hornless cow has now also been decided for regulation as a conventional organism, as well as a second genome-edited yeast strain, and in the end of November a vote on genome-edited waxy maize will take place.

Canada

Canada regulates based on the product but has a regulatory system that is unique among industrial countries, in that it regulates plants with novel traits (PNTs), regardless of the method used to develop them. A plant developed by chemical or radiation mutagenesis can be treated as a conventional variety and subject to agronomic and safety requirements, whereas a plant developed by transgenic breeding will always be treated as a PNT. However, a plant developed by mutagenesis technologies can also be treated as a PNT if the trait that is being focused on is viewed to be outside a normal band of expression. Canadian plant breeders perceive that if a

gene is modified to express higher or lower by either 30% or more, then it will be treated as a PNT, regardless of the process. There is evidence emerging that public sector breeders are taking steps in their breeding programs to scale back varieties that have traits expressing beyond the 30% self-assessed benchmark. Canada has approved two herbicide tolerant genome edited canola varieties, one in 2013 developed by ODM technology and the other in 2014 by site-directed mutagenesis (CFIA, 2013; 2014). Canada's use of the PNT regulatory trigger creates some challenges when it comes to the use of genome editing. Since the first GM canola varieties were approved for production in Canada in 1995, all GM varieties have been regulated as PNTs. This creates problems for public plant breeders, particularly because many commodity importers view PNT status as being the equivalent of GM status. For example, some universities have decided that no PNT variety research will be undertaken as to do this, dedicated, parallel systems would be required. Duplicating laboratories, phytotrons, greenhouses and field trials are expenses beyond the scope for public breeding programs. If genome editing regulations are treated as PNTs, this will most likely prohibit public sector plant breeders from using these technologies. However, the fact that the USA is treating CRISPR-Cas9 as conventional plant breeding will put pressure on Canadian regulatory agencies to ensure there is regulatory harmonization between both countries regarding genome editing regulation.

Chile

The Chilean legal framework regarding GM plants has been well described by Sánchez & León (2016). The Exent Resolution 1523/2001 establishes procedures for import, domestic propagation, and re-export of propagated GM plant material. National research and development (R&D) activities are subject to the provisions of the Resolution, including contained use to experimental field release and surveillance and a species-specific biosafety protocol (Sánchez, 2015). Hence, the regulatory framework 1523/2001 allows GM seed production exclusively for export and R&D activities, yet those seeds are not allowed to remain in the country or be locally commercialized. From the GM food/feed perspective, some rules have been issued by the Health Ministry in order to analyze, on a case-by-case basis, the approval for commercialization in Chile. However, they are not yet in place and there are not now restrictions on imports of GM products categorized as food or feed. Chile began discussing NBTs in 2016, as a result of a growing interest by several South American governments in these advances in plant biotechnology. A working table was initiated involving different governmental agencies of the Agriculture Ministry. Considering that NBTs represent an

important advance and potential for national activities, including commerce and R&D, the working group published in July 2017 general procedures for a case-by-case analysis. In general terms, the Chilean effort has focused on developing analytical procedures by which the 1523/2001 resolution could apply to the materials derived from new technology. From the analysis, if these materials are considered not subject of the normative, they should be excluded from the GM regulations and released as conventionally bred plants. The case-by-case analysis of NBT-derived products is carried out by the Forestry and Agricultural Protection Division of the Agricultural and Livestock Service (SAG). This analysis is centered on the question if a "new combination" of genetic material has occurred. The most recent understanding of "new combination" is the stable insertion of DNA fragments or coding sequences leading to gene products (proteins), elements of the RNA interference process, double strand RNA, or other sequences including information for signal peptides and/or regulatory elements. The categorization as lacking a "new combination" enables the developer (or representative) to start regular production in Chile. A consultation form is regularly used by the Protection Division of SAG. The first section covers aspects of the new material's individualization intended to be introduced to the environment (i.e. species, variety/line, phenotype description, and developer antecedents). The second section covers the process used in the development and characteristics of the technique used in the development of the individual plant and modified DNA sequences. A technical scheme for the procedure/technique (breeding pipeline) is required. The third section addresses information about previous releases and permissions in third countries.

Colombia

The Colombian Agricultural & Farming Institute (ICA) is responsible for exerting technical control over production and commercialization of agricultural and farming feedstock, animal genetic material and seed for sowing, with the purpose to prevent risks that may affect agricultural and farming health, food safety and domestic agricultural and farming production. Recently, ICA made official the Resolution No. 00029299 (https://diario-oficial.vlex.com.co/vid/resoluci-n-n-mero-736329965?_ga=2.121199179.279196541.1534802394-1753836802.1534802394). This Resolution sets forth the procedure that must be applied to crops obtained by means of using phytoimprovement innovation techniques through modern biotechnology where the final product does not contain any foreign genetic material, in order to determine if it is a Living

Modified Organism (LMO) or not and consequently decide whether the regulations on LMOs shall be applied or not.

USA

In 1986, the Office of Science and Technology Policy (OSTP) developed a Coordinated Framework for the Regulation of Biotechnology (OSTP, 1986). Using existing legal authorities, OSTP assigned three agencies – Animal Plant Health Inspection Service (APHIS), Environmental Protection Agency (EPA), and Food Drug Administration (FDA) – distinct regulatory tasks. APHIS used Plant Protection Act to regulate for plant pests and noxious weeds. EPA used Federal Insecticide Fungicide Rodenticide Act to regulate crops intended to control insects (plant-incorporated pesticides) and Toxic Substances Control Act to regulate microbes as "new chemicals." FDA used Federal Food Drug & Cosmetic Act to create a voluntary consultation process for food or feed coming from biotechnology and, in 2009, the same act to regulate DNA constructs in genetically-engineered animals as new veterinary drugs. For APHIS and FDA, regulatory approvals must comply with National Environmental Policy Act, meaning preparation of an environmental assessment or, the more detailed, environmental impact statement prior to an approval. As the EPA approval process is an equivalent evaluation, EPA does not have a separate NEPA obligation. Regarding genome-editing techniques, the question arises: how will these regulatory agencies respond to NBTs? APHIS has responded with an "Am I Regulated?" website (USDA, 2018a). From February 2017 through July 2018, APHIS responded to twenty-two inquiries and indicated that many using NBTs were not subject to APHIS regulation as plant pests or noxious weeds (USDA, 2017a; 2017b). Building on these "not regulated" determinations, the Secretary of Agriculture in March 2018 issued a statement that "USDA does not regulate or have plans to regulate plants that could otherwise have been developed through traditional breeding techniques as long as they are not plant pests or developed using plant pests." (USDA, 2018b) The Secretary referenced genome editing as falling outside APHIS regulation. Farmers in the United States are growing genome-edited crops such as herbicide-resistant canola containing a one-letter change in the genetic code. This canola is the product of a mega-nuclease breeding technique. The EPA stated that "the degree of editing … does not necessarily influence the pesticidal nature of the product" and that "knockouts could still be considered as plant-incorporated protectants" depending on the … intent of the product such as disease resistance." (EPA, 2018a) EPA intends to govern NBTs having impacts on plant diseases and insects. In June 2017, EPA approved an RNAi maize with a modification to control corn rootworm. EPA also

uses its pesticide regulations to oversee mosquitoes modified through various types of sterile insect technology (EPA, 2018b). The FDA has not declared a regulatory stance regarding foods or feeds derived from NBTs. A best guess is that FDA will apply voluntary consultation in a manner similar to the voluntary consultation for food and feed from rDNA crops. In proposed regulations (FDA, 2017), FDA asserted regulatory control over NBT animals, such as the TALENS hornless dairy cattle, as veterinary drugs. After criticism, FDA placed these proposed regulations on hold. Whether FDA will regulate NBT animals is undetermined as of July 2018. USDA-Agricultural Marketing Service has the task of adopting labels for bioengineered foods (USDA, 2018c). The Agricultural Marketing Service of USDA (AMS) has not decided whether NBTs create "bioengineered" foods, as defined in the statue, and will likely not reach a decision until December 2018.

The EU court mutagenesis ruling in an international context

A comparison to the approach of other jurisdictions

A striking similarity between the approaches taken hitherto by the countries on the American continents included in this study is the adherence to a case-by-case procedure to determine the regulatory status of a product developed by any NBT. Any similar case-by-case procedure is currently not explicitly expressed in EU legislation nor acknowledged by the CJEU mutagenesis ruling. A large coalition of organisations and associations has recently called upon the EC to identify an authority which would be capable of verifying individual cases for conformity with inclusions, exclusions or exemptions under the current GMO regulatory framework (European Initiative for Genome Editing in Plants, 2018). This would be a first prerequisite to implement a case-by-case approach for status determination, followed by establishing once and for all exactly what a GMO is according to the definition contained in the release directive. Though giving certain indications, the CJEU mutagenesis ruling does not in fact provide any conclusive and definite interpretation of the GMO definition. A way forward is either to agree on a common interpretation, or to amend the release directive in order to provide an unambiguous definition (Eriksson *et al*., 2018). Regarding the definition of a GMO, many of the American countries take a similar stance. Argentina and Chile emphasize that a new combination of genetic material, stably inherited, is required for the product to fall under the GMO regulation, and Brazil states that products not containing recombinant nucleic acids are regulated as conventional products. Colombia seems to be adopting a similar

approach. Brazil also emphasizes that products containing genetic elements that could have been obtained by conventional breeding are to be regulated as conventional products, similar to the approach by USDA. Canada´s approach is, as already explained, altogether different; however, there is an ambition to harmonize the regulations of NBTs particularly with the US. Australia, following the recent consultation, may decide to take a middle way where SDN-2, SDN-3 and ODM applications would be regulated as GMO, but SDN-1 applications not. However, the need for export-friendly regulations is also acknowledged. All of this is, in part or fully, in contrast to the CJEU ruling, which has an inclination towards a process-based interpretation of GMO in the context of mutagenesis. In the ruling, it is said that "*since […] certain of those techniques/methods involve the use of chemical or physical mutagenous agents, and others involve the use of genetic engineering, those techniques/methods alter the genetic material of an organism in a way that does not occur naturally*" (CJEU, 2018, paragraph 29) and "*It follows that organisms obtained by means of techniques/methods of mutagenesis must be considered to be GMOs within the meaning of Article 2(2) of Directive 2001/18*" (CJEU, 2018, paragraph 30). This would imply that the EU GMO regulatory framework does not explicitly acknowledge that the certain products of mutagenesis may be highly similar, or even identical, to the products of conventional breeding. There is therefore a high probability that the EU will treat, given the current legislation, the products of directed mutagenesis differently than many of its important trading partners around the world.

Trade with agricultural commodities

The ruling of the CJEU can result in significant trade disruptions. Products derived from crops that are subject to the EU GMO release directive and regulations referring to it are not allowed for import into the EU until they have been submitted for approval for import and processing. Further, in most cases these products need to be labelled as GMOs. The problem is that many of the products of directed mutagenesis are technically very challenging and costly to trace. Also, even with a manageable traceability system in place, it would not be possible to correctly identify the origin of many products, i.e. it will not be possible to provide evidence to which method has been used to develop the product. As these products might not be detectable, they are credence goods and require functioning identity preservation systems (IPS) similar to organic products (Purnhagen et al, 2018). There is however one important distinction to organic products (McCluskey et al., 2018). While the appearance of organic products in non-organic products does not matter, the appearance of GMOs in non-GMO products matters (Venus et al., 2018). As long as traders are not able to provide convincing IPS systems, international trade

can easily be blocked (Wesseler and Kalaitzandonakes, 2011). The EU imports about 32.5 million tons of soybean and soybean meal, mainly from Argentina, Brazil, and the US and about 5 million tons of rapeseed and rapeseed oil mainly from Australia, Canada, and the Ukraine. These are the markets that might soon be affected by the ruling as soybeans are in the pipeline (Table 1) and two oilseed rape varieties (canola) have reached the market in Canada and the US (Table 2). The ruling may also expose the seed companies to potential liability issues in case export restrictions caused by asynchronous approval as illustrated by the court case against Syngenta for lost export markets due to the introduction of an insect resistant corn variety in the US but not yet approved in China (Hadden Farms Inc. v. Syngenta Corp., 2014). Important to mention is also that China is an emerging big player internationally for genome edited crops. Being completely dominant when it comes to CRISPR/Cas and other patent applications, China is through heavy governmental investments gaining considerable experience with genome editing applications in rice and may sooner or later move into also many other crops (Bosma, 2018). Japan is also moving ahead with a policy on genome editing, with a governmental panel very recently announcing that the regulations governing products of genetic recombination will not apply to products in which mutations are produced at a targeted site without new genes inserted (NHK World – Japan, 2018). Apart from already existing commercial applications, there are also a large number of research applications on various crops and traits for which directed mutagenesis/genome editing tools have been applied (Schaart *et al*., 2016; Subburaj *et al*., 2016; Ricroch *et al*., 2017; Zhang *et al*., 2017; Bogdanove *et al*., 2018), not the least in Europe. It is therefore likely that many more commercial applications will reach the international market in the near future; if not developed in Europe, then elsewhere. This may result, independent of the country, in asynchronicity in approval and further may result in trade disruptions not only between the EU and its trading partners but also among other countries as mentioned above. IPS have been introduced for credence goods in food value chains with similar problems such as for organic agriculture or non-GM labelled food products (Castellari et al., 2018). Such kind of IPS may offer a solution (Venus et al., 2018) but increase costs (Kalaitzandonakes et al., 2018) that may be substantial depending on country regulations (Bovay and Alston, 2018). Harmonization of approval processes at international level might be required to avoid substantial trade disruptions (Wesseler and Kalaitzandonakes, 2011). A recent (30 Oct 2018) statement on agricultural applications of precision biotechnology that was presented by Argentina and now supported by several countries (Argentina, Australia, Brazil, Canada, Colombia, Dominican Republic, Guatemala, Honduras, Jordan, Paraguay, Uruguay, USA and Vietnam, as well as the Secretariat of the

Economic Community of West African States) in the World Trade Organisation (WTO) Committee on Sanitary and Phytosanitary Measures mentioned, amongst other things, that "*Given the differences internationally in approaches used to assess agricultural biotechnology, due consideration should be exercised by governments to avoid arbitrary and unjustifiable distinctions between end products derived from precision biotechnology and similar end products obtained through other production methods*" and "*Cooperative work by governments to minimize unnecessary barriers to trade related to the regulatory oversight of products of precision biotechnology, including the exploring of opportunities for regulatory and policy alignment, should be pursued where possible*" (WTO, 2018). This is a clear signal that the EU expeditiously needs to look over the scope of the release directive in order to align with many of the important trading partners, as the opposite can hardly be expected (i.e. that all the other countries decide to follow EU´s approach).

Reactions from the European seed sector

It was not surprising that the reactions from the European seed sector to the CJEU ruling were highly negative. The European Seed Association (ESA) declared already the same day that they see the ruling as a missed opportunity for agricultural innovation in the EU, indicating also the risk that the EU remains isolated from the rest of the world with respect to innovative agricultural developments (ESA, 2018). Some of the major seed companies also announced that they most likely will look for other markets than the European for products developed with genome editing. BASF expressed that the ruling will not affect the company much since it is run on a global platform, however that those who should worry are the European citizens who will not enjoy the benefits. Bayer, that recently purchased Monsanto, also ruled out trying to develop genome edited crops for the European market, and a comment from Syngenta was equally discouraged (Reuters, 2018). A press release from EuropaBio also raised concerns that the EU could miss out on the benefits of genome editing. The comment from Secretary General John Brennan was somewhat more cautious, saying that the necessary regulatory clarity is still lacking and that the EU and its member states now need to engage in public dialogue with their citizens about genome editing (EuropaBio, 2018). Among supporters of organic agriculture, a discussion about the potential of genome editing for addressing solutions has started and this might have an impact on policy makers (Shao et al., 2018). We agree and would add that one detail to start with is a new Eurobarometer specifically on the topic of genome editing, which would be of great help for the EC and the European Parliament (EP) to properly address the issues related to governance of precision breeding.

The aftermath of the EU court ruling – has the final word been said?

As mentioned earlier, the EU court ruling on mutagenesis indicates that the EU will subject the products of directed mutagenesis to the provisions of the release directive and the ones referring to it. However, there are some complicating factors that are currently being raised at various levels. First, neither the release directive nor the court ruling offer any tangible definition of mutagenesis. It is also a fact that some national jurisdictions within the EU approach conventional mutagenesis differently, with e.g. France in their national implementation of the release directive aligns with the GMO definition embodied in the Cartagena protocol in the sense that randomly induced mutagenesis is not considered to be GMO at all. This may have huge implications, also considering that some EU member states (such as Sweden) in their written observations to CJEU on case C-528/16 argued that the organisms resulting from directed mutagenesis should not be considered GMOs at all. It is therefore important that the EU takes action to provide a functional definition of mutagenesis, and in the process actively seeks advice from the scientific community.

Sweden also voiced some serious concerns in a letter to the EC on 1 October 2018, asking the EC to clarify the issues related to detection of plants and products resulting from new mutagenesis methods, to clarify the conditions within recital 17 of the release directive (which exempt from the directive GMOs which have conventionally been used in a number of applications and have a long safety record), and also questioning the logic in subjecting two organisms that carry exactly the same molecular changes to different risk assessment procedures. The letter also urged the EC to analyse the consequences of the CJEU ruling in relation to the WTO agreements (Swedish Board of Agriculture, 2018).

The potential problem for international trade has also been emphasized in a recent (13 Nov 2018) statement from the Chief Scientific Advisors to the European Commission (EC), which listed a number of issues and questions arising from the court ruling, such as the GMO definition, safety considerations, detection and identification issues, as well as some potential consequences. Amongst others, it is explained that application of the obligations of the GMO regulations to the products of genome editing, such as traceability and labelling, will be difficult to implement, and this problem will be exacerbated when exporting countries start to market varieties and products that are not regulated within their own jurisdictions (European Commission, 2018).

Conclusions

The negative reactions from the EU seed sector, as well as from many scientists (IPMB, 2018; EPSO, 2018), to the CJEU ruling on mutagenesis are understandable. We nevertheless here aim at providing some openings for a constructive way forward. Irrespective of the slightly problematic issue that the CJEU engaged in scientific speculation in the ruling (CJEU, 2018, paragraph 48), it is nevertheless encouraging that the ruling considers that direct modification of the genetic material through mutagenesis makes it possible to obtain the same effects (in terms of risk) as the introduction of a foreign gene. This statement makes it possible to address the issues of "conventional use in a number of applications" and "long safety record", as it can be reasonably argued that the type of products resulting from transgenesis that have had extensive commercial applications by now have a sufficiently long history of safe use. What was considered negligible risks already in the late 1980s (Young & Miller, 1987; NAS, 1987) has been proven beyond doubt to be at a level comparable to that of conventional breeding (Kuntz & Ricroch, 2012; DeFrancesco, 2013; Nicolia *et al*., 2013; Barrows *et al*., 2014; Ricroch & Kuntz, 2014; Sanchez, 2015; Castanera *et al*., 2016; Bartholomaeus, 2018; ICGEB, 2018; Ricroch *et al*., 2018). Also, what was still considered a technology *potential* 16 years ago (Dale *et al*., 2002) has now translated into extensive on-farm and environmental benefits (Carpenter, 2010; 2011; Benbrook, 2012; Green, 2012; Klumper & Qaim, 2014; Brookes, 2014; Brookes & Barfoot, 2017a; 2017b; Pellegrino, 2018). Also, there are signs that several EU countries look favourably on the commercial application of directed mutagenesis (Eriksson, 2018). Despite the regulatory gridlock that has persisted in the EU for the authorization for commercial field release for GMOs over the past 20 years (Smart *et al*., 2015), it is therefore not to be taken for granted that the products of directed mutagenesis will suffer the same fate even if they would be regulated as GMOs and if there should be any applications for authorization even in the near future. This may in fact serve to return the EU GMO regulations to the case-by-case implementation of the level of required risk assessment that was envisaged in the first GMO directive adopted in 1990.

Nevertheless; given the far-reaching consequences the CJEU ruling may have for the international trade with agricultural commodities, it is essential that the EC immediately engages in bilateral and multilateral discussions with trading partners and within the WTO on how to handle the products of directed mutagenesis in a mutually beneficial way and which will not unjustifiably hinder international trade with these products and in particular not prevent access for African countries that would greatly benefit from these technologies (Wesseler *et*

al., 2017). We, as publicly funded academic researchers or public officials, are available for policy and law makers in our respective jurisdictions to provide scientific background data in order to facilitate the development of this process in a transparent and evidence-based way.

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Author contributions

DE planned and designed the work, wrote the introduction, analysis, discussion and conclusion, and assembled the manuscript. DK, AN, BP, HP, SS and AW contributed with their respective country descriptions. KP and JW contributed with analysis and parts of the discussion. KP in addition contributed to the introduction and wrote much of the part describing the CJEU case

Disclosure

The information and views are those of the authors as individuals and experts in the field, and do not necessarily represent those of the organizations where they work.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

Figure and Table legends

Figure 1. Roadmap for the regulatory classification of new breeding techniques, including genome edited crops, in Argentina. So far, this procedure is only available for plants and animals.

Table 1. Examples of events obtained by directed mutagenesis which are in the pipeline for commercialization, and which regulatory authorities have declared to not be regulated as GMO.

Table 2. Events (non-microbial) that have been obtained by directed mutagenesis and which have been approved for commercialization in the respective jurisdiction.

References

Abdallah NA, Prakash CS, McHughen AG. 2016. Genome editing for crop improvement: Challenges and opportunities. *GM Crops Food* **6**: 183-205.

AG Bobek. 2018. Opinion of Advocate General Bobek, Case C-528/16, delivered on 18 January 2018. [WWW document] URL http://curia.europa.eu/juris/document/document.jsf?text=&docid=198532&pageIndex=0&doclang=EN&mode=req&dir=&occ=first&part=1&cid=417388 [accessed 19 June 2018].

Ahloowalia BS, Maluszynksi M. 2001. Induced mutations – a new paradigm in plant breeding. *Euphytica* **118**: 167-173.

Arora L, Narula A. (2017). Gene editing and crop improvement using CRISPR-Cas9 system. *Frontiers in Plant Science* **8:** 1932.

Barrows G, Sexton S, Zilberman D. 2014. The impact of agricultural biotechnology on supply and land-use. *Environment and Development Economics* **196**: 676-703.

Bartholomaeus A. 2018. Regulating safety of novel food and genetically modified crops. *Advances in Botanical Research*, **86**: 89-110.

Benbrook CM. 2012. Impacts of genetically engineered crops on pesticide use in the U.S. – the first sixteen years. **Environmental Sciences Europe** *24*: 24.

Berg P, Baltimore D, Boyer H, Cohen S, Davis R, Hogness DS, Nathans D, Roblin R, Watson JD, Weissman S, Zinder ND. 1974. Potential biohazards of recombinant DNA molecules. *Proc. Nat. Acad. Sci*. **71(7)**: 2593-2594.

Bogdanove AJ, Donovan DM, Elorriaga E, Kuzma J, Pauwels K, Strauss SH, Voytas DF. 2018. Genome editing in agriculture: methods, applications and governance. *CAST Issue Paper* **60**, July 2018.

Bortesi J, Fischer R. 2015. The CRISPR/Cas9 system for plant genome editing and beyond. *Biotechnological Advances* **33:** 41-52.

Bosma, R. 2018. China breeds success: The country´s head start in new breeding techniques. RaboResearch, 25 July 2018. [WWW document] URL https://research.rabobank.com/far/en/sectors/farm-inputs/china-breeds-success.html [accessed 19 August 2018].

Bovay, J, Alston J. 2018. GMO food labels in the United States: Economic implications of the new law. *Food Policy* **78**: 14 - 25.

Brinegar K, Yetisen AK, Cho S, Vallillo E, Ruiz-Esparza GU, Prabhakar AM, Khademhosseini A, Yun S-H. 2017. The commercialization of genome-editing technologies. *Critical Review of Biotechnology* **37(7):** 924-932.

Brookes G. 2014. Weed control changes and genetically modified herbicide tolerant crops in the USA 1996-2012. *GM Crops & Food* **5(4)**: 321-332.

Brookes G, Barfoot P. 2017a. Environmental impacts of genetically modified (GM) crop use 1996-2015: Impacts onpesticide use and carbon emissions. *GM Crops & Food* doi: 10.1080/21645698.2017.1309490.

Brookes G, Barfoot P. 2017b. GM crops: global socio-economic and environmental impacts 1996-2015. PG Economics Ltd, Dorchester, UK.

Carpenter J. 2010. Peer-reviewed surveys indicate positive impact of commercialized GM crops. *Nature Biotechnology* **28(4)**: 319-321.

Carpenter J. 2011. Impact of GM crops in biodiversity. *GM Crops* **2(1)**: 7-23.

Castanera P, Farinós GP, Ortego F, Andow DA. 2016. Sixteen years of Bt maize in the EU hotspot: why has resistance not evolved? *PLoS ONE* **11(5)**: e0154200.

Castellari E, Soregaroli C, Venus T, Wesseler J. 2018. Food Processor and Retailer non-GMO Standards in the US and EU and the driving role of regulations. *Food Policy*, **78**: 26-37.

CFIA. 2013. Canadian Food Inspection Agency. DD 2013-100: Determination of the Safety of Cibus Canada Inc.'s Canola (Brassica napus L.) Event 5715. [WWW document] URL http://www.inspection.gc.ca/plants/plants-with-novel-traits/approved-under-review/decision-documents/dd-2013-100/eng/1427383332253/1427383674669 [accessed 25 July 2018].

CFIA. 2014. Canadian Food Inspection Agency. Decision Document DD2014-101 Determination of the Safety of BASF Canada Inc.'s Canola (Brassica napus) Event CLB-1. [WWW document] URL http://www.inspection.gc.ca/plants/plants-with-novel-traits/approved-under-review/decision-documents/dd2014-101/eng/1454107718197/1454107776755 [accessed 25 July 2018].

Chen K, Gao C. 2014. Targeted genome modification technologies and their applications in crop improvements. *Plant Cell Reports* **33**: 575-583.

CJEU. 2018. Judgment of the Court (Grand Chamber) in case C-528/16, 25 July 2018. [WWW document] URL http://curia.europa.eu/juris/document/document.jsf?text=&docid=204387&pageIndex=0&doclang=en&mode=req&dir=&occ=first&part=1&cid=584259 [accessed 9 August 2018].

CTNBio. 2005. Ministry of Science, Technology and Innovation – MCTI - Brazilian Biosafety Law Nº 11.105, Of 24 March 2005. [WWW document] URL http://ctnbio.mcti.gov.br/en/leis [accessed 22 August 2018].

CTNBio. 2018. Normative Resolution 16 (RN16). [WWW document] URL http://ctnbio.mcti.gov.br/resolucoes-normativas [accessed 22 August 2018].

Dale PJ, Clarke B, Fontes EMG. 2002. Potential for the environmental impact of transgenic crops. *Nature Biotechnology* **20**: 567-574.

De Jong P, Bertolotto E, de Seze I. 2018. From fark to fork: the regulatory status of non-GMO plant innovations under current EU law. *Bio-Science Law Review* **16(6)**: 251-266.

DeFrancesco L. 2013. How safe does transgenic food need to be? *Nature Biotechnology* **31(9)**: 794-803.

Ding Y, Li H, Chen L-L, Xie K. 2016. Recent advances in genome editing using CRISPR/Cas9. *Frontiers in Plant Science* **7:** 703.

EPA. 2018a. U.S. Environmental Protection Agency, Regulatory Avenues at US EPA for Products of Novel Breeding Technologies (May 9, 2018). [PowerPoint].

EPA. 2018b. U.S. Environmental Protection Agency, Regulatory Updates Novel Mosquito Products: Wolbachia and Oxitec GE Mosquito (May 2, 2018). [PowerPoint].

EPSO. 2018. On the ECJ ruling regarding mutagenesis and the Genetically Modified Organisms Directive. First reaction, 26 July 2018 [WWW document] URL http://www.epsoweb.org/webfm_send/2405 [accessed 19 August 2018].

Eriksson D. 2018. The Swedish policy approach to directed mutagenesis in a European context. *Physiologia Plantarum* doi.org/10.1111/ppl.12740.

Eriksson D, Harwood, W, Hofvander P, Jones H, Rogowsky P, Stöger E, Visser R. 2018. A welcome proposal to amend the GMO legislation of the EU. *Trends in Biotechnology* doi.org/10.1016/j.tibtech.2018.05.001.

ESA. 2018. Case C-528/16 reaction: A bleak view for agricultural innovation in the EU. European Seed. [WWW document] URL http://european-seed.com/2018/07/a-bleak-view-for-agricultural-innovation-in-the-eu/ [accessed 19 August 2018].

EuropaBio. 2018. Court ruling could lock out the benefits of genome editing from Europe. EuropaBio, press release 25 July 2018. [WWW document] URL http://www.europabio.org/cross-sector/publications/court-ruling-could-lock-out-benefits-genome-editing-europe [accessed 19 August 2018].

European Commission. 2018. A scientific perspective on the regulatory status of products derived from gene editing and the implications for the GMO Directive. Statement by the Group of Chief Scientific Advisors, 13 November 2018.

European Initiative for Genome Editing in Plants. 2018. Open Letter to Commission President Juncker, Commissioner for Health Andriukaitis, Commissioner for Agriculture Hogan, Commissioner for Research, Science and Innovation Moedas, and Commissioner for Jobs, Growth, Investment and Competitiveness Katainen. [WWW document] URL https://cdn.website-editor.net/ed25e686182040aeb41d3b3d05cc2cd2/files/uploaded/Open%2520letter.pdf [accessed 9 August 2018].

FDA. 2017. U.S. Food & Drug Administration, 2017. Draft Guidance # 187, Regulation of Intentionally Altered Genomic DNA in Animals. *Federal Register* **82**: 6562.

Georges F, Ray H. 2017. Genome editing of crops: A renewed opportunity for food security. *GM Crops & Food* **8(1):** 1-12.

Green JM. 2012. The benefits of herbicide-resistant crops. *Pest Management Science* **68**: 1323-1331.

Hadden Farms Inc. v. Syngenta Corp. 2014. No. 3:14-cv-03302-SEM-TSH (C.D. Ill. filed Oct. 3, 2014) (class action complaint for damages and injunctive relief). [WWW document] URL http://www.fien.com/pdfs/IllinoisvSyngenta.pdf ("Syngenta Corn Class Action") [accessed 9 August 2018].

Hartung, F, Schiemann J. 2014. Precise plant breeding using new genome editing techniques: opportunities, safety and regulation in the EU. *The Plant Journal* **78**: 742-752.

Hilscher J, Buerstmayer H, Stöger E. 2017. Targeted modification of plant genomes for precision crop breeding. *Biotechnology Journal* **12**: 1600173.

HLG-SAM. 2017. New techniques in agricultural biotechnology. Explanatory Note 02. European Commission High Level Group of the Scientific Advisory Mechanism, Brussels.

ICGEB. 2018. [WWW document] URL http://bibliosafety.icgeb.org/ [accessed 9 August 2018].

IPMB. 2018. Immediate review of the ECJ ruling on plant genome editing. Petition. [WWW document] URL https://www.change.org/p/ipmb2018-immediate-review-of-the-ecj-ruling-on-plant-genome-editing-9ff3df10-9f7d-44de-b379-8a01a1d71ba2?recruiter=893799704&utm_campaign=signature_receipt&utm_medium=twitter&utm_source=share_petition [accessed 19 August 2018].

Jansson S. 2018. Gene-edited plants on the plate - the "CRISPR cabbage story". *Physiologia Plantarum* doi: 10.1111/ppl.12754.

Kalaitzandonakes, N, Lusk J, Magnier A. (2018). The price of non-genetically modified (non-GM) food. *Food Policy* **78**: 38 - 50.

Klumper W, Qaim M. 2014. A meta-analysis of the impacts of genetically modified crops. *PLoS ONE* **9(11)**: e111629.

Krämer, L. 2015. Legal questions concerning new methods for changing the genetic conditions in plants. [WWW document] URL http://www.testbiotech.org/sites/default/files/Kraemer_Legal%20questions_new%20methods_0.pdf [accessed 19 June 2018].

Kuntz M, Ricroch AE. 2012. Is it time to adjust the current regulatory risk assessment for GM food and feed? *ISB News Report* February 2012.

NAS. 1987. Introduction of recombinant DNA-engineered organisms into the environment: key issues. Council of the National Academy of Sciences, National Academy Press, Washington, D.C.

NHK World – Japan. 2018. Govt. panel to not regulate some genome editing. [WWW document] URL https://www3.nhk.or.jp/nhkworld/en/news/20180821_14/ [accessed 21 August 2018].

Nicolia A, Manzo A, Veronesi F, Rosellini D. 2013. An overview of the last 10 years of genetically engineered crop safety research. *Critical Reviews in Biotechnology*, **34(1)**: 77-88.

OSTP 1986. U.S. Office of Science and Technology Policy, Coordinated framework for regulation of biotechnology. *Federal Register* **51**:23302-23350.

Paul III JW, Qi Y. 2016. CRISPR/Cas9 for plant genome editing: accomplishments, problems and prospects. *Plant Cell Reports* **35:** 1417-1427.

Pellegrino E, Bedini S, Nuti M, Ercoli L. 2018. Impact of genetically engineered maize on agronomic, environmental and toxicological traits: a meta-analysis of 21 years of field data. *Scientific Reports*, **8**: 3113.

Pennisi E. 2016. The plant engineer. *Science* **353(6305)**: 1220-1224.

Punt, M, Wesseler J. 2016. Legal but costly: An analysis of the EU GM regulation in the light of the WTO trade dispute between the EU and the US. *World Economy* **39(1)**:158-169.

Purnhagen K, Rebasti E. 2007, Judge's Empire? Interview with Rudolf Bernhardt. *European Journal of Legal Studies* **1**: 13-21.

Purnhagen KP, Kok E, Kleter G, Schebesta H, Visser RGF, Wesseler J. 2018a. The European Union Court´s Advocate General´s opinion and new plant breeding techniques. *Nature Biotechnology* **36(7)**: 1-2.

Purnhagen K, Kok E, Kleter G, Schebesta H, Visser RGF, Wesseler J. 2018b. EU Court casts new plant breeding techniques into regulatory limbo. *Nature Biotechnology* **36(7)**: in print.

Reuters. 2018. Bayer, BASF to pursue plant gene editing elsewhere after EU ruling. [WWW document] URL https://www.reuters.com/article/us-eu-court-gmo-companies/bayer-basf-to-pursue-plant-gene-editing-elsewhere-after-eu-ruling-idUSKBN1KH1NF [accessed 19 August 2018].

Ricroch A, Kuntz M. 2014. Looking back at safety assessment of GM food/feed: an exhaustive review of 90-day animal feeding studies. *International Journal of Biotechnology* **13(4)**: 230-256.

Ricroch A, Clairand P, Harwood W. 2017. Use of CRISPR systems in plant genome editing: toward new opportunities in agriculture. *Emerging Topics in Life Sciences* **1**: 169-182.

Ricroch A, Akkoyunlu S, Martin-Laffon J, Kuntz M. 2018. Assessing the environmental safety of transgenic plants: honey bees as a case study. *Advances in Botanical Research* **86**: 111-167.

Samanta MK, Dey A, Gayen S. 2016. CRISPR/Cas9: an advanced tool for editing plant genomes. *Transgenic Research* **25:** 561-573.

Sánchez MA. 2015. Conflicts of interests and evidence base for GM crops food/feed safety research. *Nature Biotechnology* **33(2)**: 135-137.

Sánchez M, León G. 2016. Status of market, regulation and research of genetically modified crops in Chile. *New Biotechnology* **33**:815-823.

Schaart JG, van de Wiel CCM, Lotz LAP, Smulders MJM. 2016. Opportunities for products of new plant breeding techniques. *Trends in Plant Science* **21(5)**: 438-449.

SAG. 2017. Servicio Agrícola y Ganadero, Letter 4968, August 2017. [WWW document] URL https://www.fruit-tree-genomics.com/documents-1 [accessed 4 December 2018].

SAG. 2018. Servicio Agrícola y Ganadero, Resolution Number 415, January 2018. [WWW document] URL https:// www.fruit-tree-genomics.com/documents-1 [accessed 4 December 2018].

Shao Q, Punt M, Wesseler J. 2018. New Plant Breeding Techniques Under Food Security Pressure and Lobbying. *Frontiers in Plant Science* **9**: 1324.

Smart RD, Blum M, Wesseler J. 2015. EU Member States' Voting for Authorizing Genetically Engineered Crops: a Regulatory Gridlock. *German Journal of Agricultural Economics* **64**: 244-262.

Smart RD, Blum M, Wesseler J. 2017. Trends in Genetically Engineered Crops' Approval Times in the United States and the European Union. *Journal of Agricultural Economics* **68(1)**: 182-198.

Songstad DD, Petolino JF, Voytas DF, Reichert NA. 2017. Genome editing of plants. *Critical Review in Plant Science* **36(1):** 1-23.

Spranger TM. 2015. Legal Analysis of the applicability of Directive 2001/18/EC on genome editing technologies. [WWW document] URL https://bfn.de/fileadmin/BfN/agrogentechnik/Dokumente/Legal_analysis_of_genome_editing_technologies.pdf [accessed 19 June 2018].

Sprink T, Eriksson D, Schiemann J, Hartung F. 2016. Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts. *Plant Cell Reports* **35**: 1493-1506.

Stella S, Montoya G. 2016. The genome editing revolution: A CRISPR-Cas TALE off-target story. *Bioessays* **38:** S4-S13.

Subburaj S, Tu L, Jin Y-T, Bae S, Seo PJ, Jung YJ, Lee G-J. 2016. Targeted genome editing, an alternative tool for trait improvement in horticultural crops. *Horticultural and Environmental Biotechnology* **57(6)**: 531-543.

Swedish Board of Agriculture. 2018. Follow-up from PAFF-meeting on September 11, 2018. Letter to the European Commission, Dnr 5.1.21-124/18.

USDA. 2017a. USDA-APHIS Response Letter to Dr Karen Bohmert-Tatarev, Confirmation of Regulatory Status of a Genome-Edited Camelina Line Developed by CRISPR/Cas Technology. 29 August 2017.

USDA. 2017b. USDA-APHIS Response Letter to Dr. Shaun Curtin, Confirmation that a Glycine max (soybean) line mutagenized using CRISPR-Cas9 is not a regulated article. 16 October 2017.

USDA. 2018a. USDA-APHIS. Am I regulated under 7 CFR Part 340?. [WWW document] URL https://www.aphis.usda.gov/aphis/ourfoucus/biotechnology/am-i-regulated [accessed 31 July 2018].

USDA. 2018b. United States Department of Agriculture, Press Release No. 0070.18. 28 March 2018.

USDA. 2018c. USDA-Agricultural Marketing Service (AMS). Proposed Rule, National Bioengineered Food Disclosure Standard, *Federal Register* **83**:19860-19889.

Venus T, Drabik D, Wesseler J. 2018. Non-GMO Food Labeling in Germany – From a Niche to Mainstream? *Food Policy*, **78**: 58-67.

Volpi e Silva N, Patron NJ. 2017. CRISPR-based tools for plant genome engineering. Emerging Topics in Life Science doi: 10.1042/ETLS20170011.

Waltz E. 2018. With a free pass, CRISPR-edited plants reach market in record time. *Nature Biotechnology* **36(1)**: 6-7.

Wasmer M, Robienski J. 2018. Which organisms and technologies fall under the mutagenesis exemption of the European GMO-Directive? *Journal of Consumer Protection and Food Safety* **13:** 323-327.

Wesseler, J Smart, R Thomson J, Zilberman D. 2017. Foregone benefits of important food crop improvements in Sub-Saharan Africa. *PLoS ONE* **12(7)**: e0181353.

Wesseler J, Kalaitzandonakes N. 2011. Present and Future EU GMO policy. In Arie Oskam, Gerrit Meesters and Huib Silvis (eds.), EU Policy for Agriculture, Food and Rural Areas. Second Edition, pp. 23-323 – 23-332. Wageningen: Wageningen Academic Publishers.

Whelan A, Lema M. 2015. Regulatory framework for gene editing and other new breeding techniques (NBTs) in Argentina. *GM Crops & Food* **6**: 253-265.

WTO. 2018. International statement on agricultural applications of precision biotechnology. Communication from Argentina, Australia, Brazil, Canada, Guatemala, Honduras, Paraguay and the United States of America. World Trade Organisation, Committee on Sanitary and Phytosanitary Measures. G/SPS/GEN/1658/Rev.2, 30 October 2018.

Yin K, Gao C, Qiu J-L. 2017. Progress and prospects in plant genome editing. *Nature Plants* **3:** 17107.

Young FE, Miller HI. 1987. Hazards of genetic engineering. *Nature* **326**: 326.

Zhang K, Raboanatahiry N, Zhu B, Li M. 2017. Progress in genome editing technology and its application in plants. *Frontiers in Plant Science* **8**: 177.