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CONFERENCE REPORT

An overview of regulatory approaches to genome editing in agriculture

KEYWORDS
Genome editing;
Trade and agriculture;
Biotechnology;
Safety assessment;
Technology regulation

Abstract The ''*OECD Conference on Genome Editing: Applications in Agriculture – Implications for Health, Environment and Regulation*'', brought together policy makers, academia, innovators and other stakeholders involved in the topic, in order to take stock of the existing research and applications of genome editing, and to thereby provide science-based input to the discussion of the potential impact of genome editing in the context of overarching agricultural and food policies. The conference provided a timely opportunity for information exchange between scientific experts, risk assessors, policy makers, regulators, private sector innovators and other stakeholders from around the world. In this paper, we summarise the conference session on the ''*Regulatory aspects*'' concerning genome editing (*Session 3*), during which government representatives from six different countries around the world reported on the policy frameworks pertaining to genome editing in their respective countries, and discussed their specificities, as well as the common issues encountered.

Background

Genome editing refers to techniques, in which specialised enzymes that have been modified can insert, replace, or remove DNA from a genome with a high degree of specificity; the techniques represent the latest innovation in the toolbox of genetic engineering/modification (GE/GM) methods. Especially the most discussed genome editing system known as CRISPR/Cas9 (i.e. ''Clustered Regularly Interspaced Short Palindromic Repeats'', using the CRISPR-associated protein 9) has received wide-spread application, because it enables the development of easily deployable low-cost tools for innovation in biomedicine, agriculture, industrial biotechnology and other sectors relating to the bioeconomy.

It is important to highlight that up to three types of genome editing can be distinguished (see Table 1); each one of these types poses specific challenges to the regulatory considerations pertaining to it, and could thus induce technique-specific discrepancies in the relevant governance approaches.

The revolutionary impact of genome editing has already been demonstrated on a wide variety of agricultural organisms; its successful applications range from the improvement of the efficiency of plant and animal breeding, to the introduction of new methods for the control of pests and diseases. This rapidly growing deployment of genome editing, however, causes implications on policies pertaining to the technology.

These policy implications raised by genome editing were discussed at a dedicated ''*Conference on Genome Editing: Applications in Agriculture – Implications for Health, Environment and Regulation*'', held by the intergovernmental Organisation for Economic and Co-operative Development (OECD) on 28–29 June 2018 in Paris.[2]

The conference, which brought together over 200 participants from 35 countries, aimed to highlight existing research and applications of genome editing in the agricultural sector, in order to provide science-based input to the discussion of the potential impact of genome editing in the context of overarching agricultural and food

[2] The full conference programme can be found here: http://www.oecd.org/environment/genome-editing-agriculture/oecd-conference-on-genome-editing-programme.pdf.

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2452-0721/

Table 1 Four types of genome editing need to be distinguished, especially with regard to potential discrepancies in the regulatory approaches to the techniques and/or their products.

Genome editing type	Description
SDN1[a]	Involves the unguided repair of a targeted double-strand break (DSB) by the mechanism called nonhomologous end joining. The spontaneous repair of this break can lead to a mutation causing gene silencing, gene knock-out or a change in the activity of a gene. Efficient method, with many applications already.
SDN2[a]	Involves a template-guided repair of a targeted DSB using a sequence donor, typically short single-stranded DNA. The donor carries one or several small mutations flanked by two sequences matching both ends of the DSB, and is thus recognised as a repair template, allowing the introduction of the mutation(s) at the target site. The efficiency of the technique is lower than SDN1, but strongly varies according to the species, donor design, the time and method of delivery, and other conditions.
SDN3[a]	Involves a template-guided repair of a targeted DSB using a sequence donor, typically double-stranded DNA containing an entire gene or an even longer genetic element(s). Both ends of the donor are homologous to the DSB ends (usually more than 800 bp each), which therefore recognise the donor as a repair template, allowing the introduction of the gene or genetic element(s) at the target site. Efficiency is lower than SDN1, but strongly varies according to the species, donor design, the time and method of delivery and other conditions.

Adapted from Ricroch (2019) and Friedrichs et al. (2019).
[a] SDN: site-directed nuclease.

policies, such as those pertaining to global food safety and security, sustainability, and climate change adaptation. In doing so, the conference provided a timely opportunity for information exchange between scientific experts, risk assessors, policy makers, regulators, private sector innovators and other stakeholders from around the world. The policy considerations discussed at the conference have been published in Friedrichs et al. (2019), and a detailed meeting report of the conference can be found in Friedrichs, Takasu, et al. (2019); it needs to be noted that the OECD conference did not intend to deliver recommendations regarding the governance of genome editing, because any potential initiation for policy development or harmonisation activities continues to fall to the relevant OECD Committees and governments.

Regulatory considerations of genome editing around the world

The OECD conference commenced with a fact-finding session that highlighted and discussed the *''Applications of genome editing in agriculture – plant and animal breeding''* (*Session 1*), and subsequently summarised and debated on the *''Risk and safety considerations''* arising from these technological applications (*Session 2*). The conference culminated in a discussion of the *''Regulatory aspects''* concerning genome editing (*Session 3*), during which government representatives from six different countries around the world reported on the policy frameworks pertaining to genome editing in their respective countries. The representatives addresses the regulatory status of agricultural technologies in their respective countries, explaining the regulatory approaches to genome editing domestically, as well as the relevant socio-political background influencing them; they detailed the underlying legal definitions of GE/GM in relation to genome editing and risk assessment considerations, and highlighted the resulting considerations regarding the safety of plant breeding practices and existing regulations of agricultural products.

The presenters characterised three main regulatory approaches to the governance of genome editing (Friedrichs et al., 2019); the findings have been illustrated in Fig. 1:

1. **(Review of) existing process-triggered GE/GM regulatory systems**: Australia, New Zealand, Europe, and India are using a process-driven regulatory trigger to regulate GE/GM organisms; these jurisdictions reported to be currently reviewing the scope of their regulatory definitions, in order to clarify, if all forms of genome editing fell under their respective existing GE/GM regulatory framework.
2. **Existing product-triggered regulations**: Canada and the United States are regulating GE/GM and genome editing products according to a product-trigger, under which the relevant novelty of the trait in question was considered

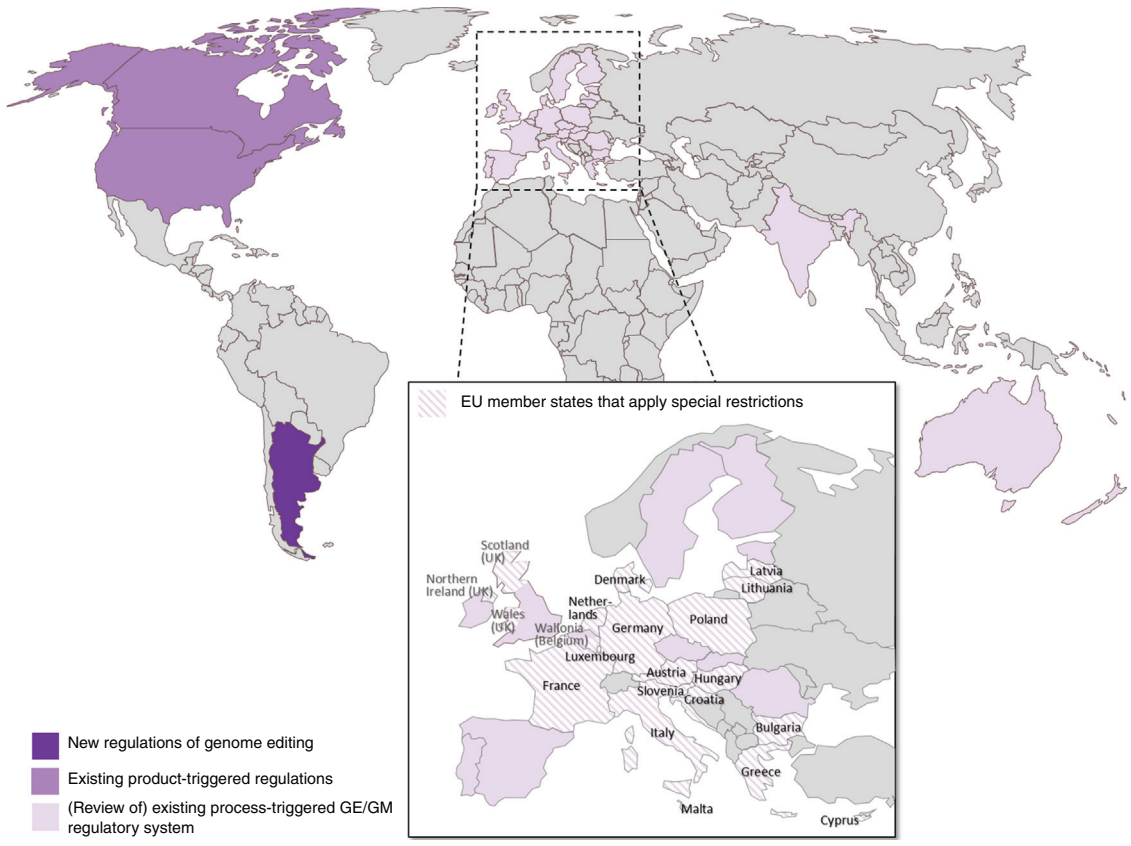

Figure 1 Selected countries and regions that presented and discussed their regulatory frameworks for genome editing at the OECD Conference (28–29 June 2018); the inset illustrates the 19 EU Member States that have filed ''demands for restriction of the geographical scope of a GMO application or authorisation'' (see Table 2).

on a case-by-case basis, irrespective of the technology used to develop it.

3. **New regulations of genome editing**: Argentina reported to introduced a new, bespoke regulatory resolution on New (Plant) Breeding Techniques (N(P)BTs) in 2015, making it one of the first countries to have passed a regulation on this novel set of techniques, covering the sub-category of genome editing in their course.

A detailed description of the relevant applicable regulations in those countries that are illustrated in Fig. 1 can be found in Table 2.

Subsequent to the country-specific presentations of the current regulatory approaches to genome editing, the government representatives participated in a panel debate, which sought to discuss the regulatory considerations for genome editing applications that had been identified during the session, and outlined the similarities and differences. It also considered the issues arising from a lack of global harmonisation in the regulation of genome-edited applications (Friedrichs, Takasu, et al., 2019).

It was noted that the balanced communication on and transparent discussion of both the potential risks and benefits of genome editing played a pivotal part in any governance activity, because market acceptance played an all-deciding role. While there was a strong call to base risk communication on science, it was noted that the traditional ''deficit model'', which assumed that laypeople just needed to be given enough information to come around to understanding and supporting the technology, was too simple an action and did not provide an adequate way forward.

The conference agreed that more effort was needed from all stakeholders to improve and prioritise both the communication and the information exchange concerning genome editing, in order to ultimately create a market for the technology's beneficial products: public risk communication by both advocates and opponents needed to be fact- and science-based, without over-burdening non-specialist public with undue information (Friedrichs et al., 2019).

In addition, regulators and risk assessors should review their approaches of responding to the increasing complexity of novel technologies with escalating information requirements; risk-tiering approaches suggested, and some government representatives confirmed that such methods were being considered.

Disclaimer

The opinions expressed and arguments employed in this paper are the sole responsibility of the authors and do not necessarily reflect those of the OECD or of the governments of its member countries.

Table 2 Details of the regulatory framework (review) in the countries illustrated in Fig. 1.

Country	Details of the regulatory framework (review)
New regulations of genome editing	
Argentina	Regulation of GMOs and NBTs in Argentina: • Regulatory framework based on the country's membership of a number of international groups and committees (incl. FAO/WHO/CODEX,[a] WTO/SPS,[b] FAO/IPPC[c]), combined with its current effort to ratify the Cartagena Protocol (2000) (Secretariat of the Convention on Biological Diversity 2000) • Adapts the corresponding definition for ''Living Modified Organisms'' of the Cartagena Protocol[d]: *''()...organism that possesses a novel combination of genetic material obtained through* ... in vitro *rDNA (techniques) and direct injection of nucleic acid into cells.''* • Passed a resolution on NBTs in 2015 (i.e. 173/2015); this new regulatory approach is based on the components below: 1. All NBTs involve recombinant DNA techniques, which leads to the presumption of GMOs. 2. If the NBT does not have a new combination of genetic material (e.g. does not use a transgene/uses a transgene which is removed in the final product), a non-GM regulatory classification is applied: this line-by-line process can be applied to both real products and hypothetical products; it asks basic information on the overall breeding process, genetic changes, traits, bred-out of helper transgenes, etc. 3. If the NBT has a new combination of genetic material (e.g. uses a transgene which remains in the final product), the regulatory classification stipulates that the final product falls under GM classification. Socio-economic factors: • Argentina commercialises GM crops since 1996 (i.e. it was one of the ''six founder'' countries) • Argentina represents the 3rd largest grower of GE/GM crops with 23 Mio ha • Argentina is the world's 1st ranking exporter of soya oil and meal, the 2nd of corn grain and the 3rd of soy grain • Since the launch of the NBT resolution, 12 cases had been looked at, the majority of which was at the hypothetical design stage • The origin of applicants for NBT classification differed notably from the that of the conventional GM classification: the latter had been dominated by (foreign) large multinationals, while the majority of the former originated from (local) public research institutions and small and medium-sized enterprises

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)

Existing product-triggered regulations

Canada

Regulation of GE/GM and Genome Editing in Canada:

- Canada follows a product-triggered, risk-based regulatory approach
- Biotechnology-related regulatory oversight in Canada is rather complex (i.e. no fewer than eight acts and policies, administered by eight agencies, apply to the different aspects of biotechnology products on the Canadian market):

Lead	Product	Regulation
Canadian Food Inspection Agency	Livestock feed	*Feeds Act*
	Seeds	*Seeds Act*
	Fertiliser	*Fertilizers Act*
	Veterinary biologics	*Health of Animals Act*
Health Canada (HC)	Pesticides	*Pest Control Products Act*
	Novel foods, drugs, and biologics, medical devices	*Food and Drugs Act*
ECCC, HC, DFO	Animals and all other substances	*Canadian Environmental Protection Act*
AAFC, GAC, ISED	Non-regulatory considerations	*Market Access, Industrial Policy, socio-economic impacts, trade*

ECCC (Environment & Climate Change Canada), DFO (Fisheries & Oceans Canada), AAFC (Agriculture & Agri-Food Canada), GAC (Global Affairs Canada), ISED (Innovation, Science& Economic Development Canada)

- Canada requires a *pre-market safety assessment* for agriculture biotechnology products, including products produced through gene editing, only if they are novel (i.e. express a new characteristic) and could therefore pose a *new risk*.
- Canada does not require *pre-market safety assessment* for gene edited products that do not express a novel trait (i.e. ''novel'' means ''novel to the Canadian environment, or the food or feed supply in Canada'').
  - ◯ Canada has flexible information requirements that are (a) not prescriptive, (b) case-specific, and (c) outcome-based.
- Proponents are encouraged to contact regulatory authorities early in the product development process to discuss:
  - ◯ Potential regulatory requirements (pre-submission consultations)
  - ◯ Novelty determination.

Current review activities:

- Canada identified some policy challenges raised by genome editing, and is currently following established consultation and feedback procedures, in order to solve potential problems of regulatory asymmetry

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)
United States	Regulation of GE/GM and Genome Editing in the United States: • The US applies a product-triggered regulation under existing laws to all biotechnology products, providing a network of agency jurisdictions • 2015: initiation of a modernisation of the regulatory system for biotechnology products; aim: *''[e]nsure public confidence in the regulatory system and improve transparency, predictability, coordination, and efficiency of the regulatory system''*. ◯ The review resulted in two key documents: ■ *2017 Update to the Coordinated Framework*,[e] and ■ *2016 National Strategy for Modernizing the Regulatory System for Biotechnology Products*[f] • Recent call to action from the current US Administration: *''[t]o identify legislative, regulatory, and policy changes to promote agriculture, economic development, job growth, infrastructure improvements, technological innovation, energy security, and quality of life in rural America.''* ◯ Recommendations by the Interagency Task Force on Agriculture and Rural Prosperity include ''Harnessing Technological Innovation'', in which developing a streamlined, science-based regulatory policy for biotechnology is aimed. US Department of Agriculture (USDA): • USDA Animal and Plant Health Inspection Service (APHIS) regulates biotechnology products through the control movement (i.e. permits for, or notifications of, import, interstate movement, and environmental release) of regulated articles (living organisms that had been genetically engineered and involving plant pest as a donor, recipient or a vector). • Under the *''Am I regulated'' (AIR)* process, APHIS encouraged developers to submit letters of inquiry, if they are not sure that their product falls under the relevant regulation.[g] • 2018: the US Secretary of Agriculture issued a statement to clarify *''USDA's oversight of plants produced through innovative new breeding techniques, including techniques called 'genome editing'''*: ◯ *''[The statement] does not change the existing USDA-APHIS biotech regulation (7 CFR Part 340).''* ◯ *''Many genome edited plants do not meet the regulation criteria to be subject to this regulation''*. ◯ *''[o]rganisms with the following alterations would not be considered regulated under the USDA proposed approach: deletions, single-base-pair substitutions, introduction of sequences from sexually compatible plant relatives and complete null segregants.''* US Food and Drug Administration (US FDA): • The regulatory status of a food (and feed) in the US is *''dependent upon the objective characteristics of that food, independent of the methods used to develop the food''*. ◯ The basic underlying policy has been outlined in a 1992 Statement: ■ *''Section 409 - Food Additives:* • *New components of food will be regulated as additives if they are not generally recognized as safe (GRAS), subject to certain exceptions;* • *Food additives require premarket review and approval before they can be lawfully marketed. The safety standard for use of a food additive is reasonable certainty of no harm under the conditions of intended use in food;* • *In order for use of a substance to be GRAS:* • *There must be reasonable certainty of no harm under the conditions of intended use and general recognition of that fact''* • The regulation of genetically engineered animals subject to: ◯ *Federal Food, Drug, and Cosmetic Act (FD&C Act), new animal drug provisions;* ◯ *National Environmental Policy Act (NEPA); and* ◯ *2009 FDA Guidance for Industry (GFI) #187 (revised in 2017 to cover genome edited animals – DRAFT)*: genome edited animals are evaluated as new animal drugs for the safety and effectiveness of the application

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)
	US Environmental Protection Agency (US EPA): • 2001: EPA exempts plant-incorporated protectants (PIPs) from sexually compatible plants that occurred naturally in the plant or that were moved through conventional plant breeding (40 CFR 174.25) from the United States Federal Insecticide, Fungicide, and Rodenticide (FIFRA) requirements (for example, for product registration/licensing and field testing). • 2001: EPA exempts residues of PIPs from sexually compatible plants that occurred naturally in the plant or that were moved through conventional plant breeding (40 CFR 174.508) from the United States Federal Food, Drug and Cosmetic Act (FFDCA) tolerance requirements (for example, for pesticide residues in food or feed, provided the residues are not present in food at levels that are injurious or deleterious to human health). Current review activities: USDA: • Reports commissioned and published concerning genome editing: ◯ 2016: *Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values*[h] ◯ 2017: *Preparing for Future Products of Biotechnology*[i] US FDA: • January 2017: launches two public consultations on: ◯ *(a) its regulatory approach to genome-edited plant-derived foods, and* ◯ *(b) application of genome editing to animals.* ◯ the commenting period has ended and FDA is now working on a clarification of its approach. US EPA: • EPA is evaluating the extent to which the current exemptions (i.e. 40 CFR 174.25, and 40 CFR 174.508) covered genome edited PIPs and considering approaches to clarify the regulatory status of these materials. Socio-economic factors: • In 2017, the cumulative number of APHIS-authorised permits or notification had exceeded 350 concerning genome edited articles (incl. TALEN, ZFN, CRISPR), which included *Agrobacterium* vectors in many cases.
(Review of) existing process-triggered GE/GM regulatory systems	
Australia	Australian GMO (genetically modified organisms) regulation: • In 2000: introduced the *Gene Technology Act 2000 (GT Act (2000))* ◯ Follows a process-trigger: *''GMO = an organism modified by gene technology''* (with *''gene technology = any technique for modification of genes or other genetic material''*) • In 2001: introduced the *Gene Technology Regulations (GT Regulations (2001))* ◯ Stipulates, which techniques are not gene technologies: ◯ *''Schedule 1A – Techniques that are not gene technology:* • *Radiation and chemical mutagenesis* • *Somatic cell nuclear transfer, protoplast fusion* • *A natural process not involving genetically modified material)''* ◯ *''Schedule 1 – Organisms that are not GMOs:* • *An organism that results from an exchange of DNA if: (a) the donor species is also the host species; and (b) the vector DNA contains no heterogeneous DNA''* • Intergovernmental Gene Technology Agreement between the Federal, State and Territory governments of Australia

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)
	Current review activities: • Fundamental point of uncertainty: based on the definition of GMOs alone, it is not clear, if *''a mutant, in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species)''* was a GMO or not • October 2016: the Australian OGTR initiated Technical Review of the *GT Regulations 2001*,[j] which had resulted in some proposed amendments[k]: ◯ *''Regarding new technologies, option 3 best supports the effectiveness of the legislative framework at this time. Under option 3 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. These would continue to be regulated under this option.''* ◯ *''Regarding RNAi, it was proposed to list the application of RNA molecules to induce RNAi as a technique that is not gene technology provided the RNA cannot give rise to changes to genomic sequence and cannot be translated into proteins. RNAi techniques which involve inserting sequences into the genome or use of viral vectors would continue to result in GMOs which are subject to regulation.''* ◯ *''Regarding gene drives, it was proposed to require a licence for all contained dealings with gene drive GMOs. Advice on the current regulatory status of gene drive GMOs was published on the OGTR website in December 2016.''* • July 2017: commencement of a review of the *GT Act* and the *GT Scheme*[l] to progress broader policy considerations of new technologies. The Review recommends: ◯ A process-based trigger be maintained as the entry point for the Scheme at the present ◯ The introduction of additional risk-tiering into the Scheme, to facilitate flexibility of the regulatory Scheme, and ensure: ■ The level of regulation remains proportionate to risk, and protects against under-regulation and over-regulation; and ■ Where appropriate, there is flexibility to move organisms between categories, based on identification of new risks, a history of safe use, or other relevant factors. • February 2018: the Australian OGTR (Office of the Gene Technology Regulator) publish a general advice on the coverage of new technologies[m]
Australia & New Zealand (food)	Regulation of food in Australian and New Zealand: • Australia and New Zealand share a food regulatory system; organisms fall under the relevant separate regulations of both countries • The Food Standards Australia and New Zealand (FSANZ)[n] develops standards under the Australian New Zealand Food Standards Code (the Code) • The definition for gene technology in the Code is based on recombinant DNA techniques – i.e. a process-based trigger Current review activities: • June 2017: FSANZ initiated a review of the Code, due to the *''ambiguity, if recent SDN1 and SDN2 types of edits and null segregants fell within the scope of the Standard 1.5.2 – on Food produced using gene technology''*[o]

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)
European Union[p,q]	Regulatory framework for GMOs in the European Union (EU): • *''Precautionary approach imposing a pre-market authorisation for any GMO to be placed on the market and a post-market environmental monitoring for any authorised GMO''*[r] • Overarching *''Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC''*[s]: ◯ *''Definitions: [...]* ◯ *(1) 'organism' means any biological entity capable of replication or of transferring genetic material;* ◯ *(2) 'genetically modified organism (GMO)'means 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; [...]''* • Recent ruling of the Court of Justice of the European Union (CJEU) (Case C-528/16) (ruling issued 25th July 2018): ◯ *''[...] organisms obtained by mutagenesis are GMOs within the meaning of the GMO Directive, in so far as the techniques and methods of mutagenesis alter the genetic material of an organism in a way that does not occur naturally. It follows that those organisms come, in principle, within the scope of the GMO Directive and are subject to the obligations laid down by that directive.''* ◯ *''the GMO Directive [...] does not apply to organisms obtained by means of certain mutagenesis techniques, namely those which have conventionally been used in a number of applications and have a long safety record.''* ◯ *''the Member States are free to subject such organisms, in compliance with EU law (in particular the rules on the free movement of goods), to the obligations laid down by the GMO Directive or to other obligations.''* • Overarching: *''Directive (EU) 2015/412 of the European Parliament and of the Council of 11 March 2015 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory (Text with EEA relevance)''*[t] ◯ *''this directive gives Member States more flexibility to decide on the cultivation of genetically modified crops, under certain conditions, at two distinct points in time''*[r]: ◯ *''during the authorization procedure: a Member State can ask to amend the geographical scope of the application to ensure that its territory will not be covered by the EU authorisation;''* ◯ *''after a GMO has been authorized: a Member State may prohibit or restrict the cultivation of the crop based on grounds related amongst others to environmental or agricultural policy objectives, or other compelling grounds such as town and country-planning, land use, socio-economic impacts, co-existence and public policy''* • Food- and feed-specific: *''Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (Text with EEA relevance)''*[u]: ◯ This regulation lays down a procedure for issuing decisions granting or rejecting authorisations for the placing on the market of genetically modified food and feed as well as for cultivation for the production of food and feed.[r] EU Member State specific provisions: • Since introduction of the *''Directive (EU) 2015/412 of the European Parliament and of the Council of 11 March 2015 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory''*, EU Member States are no longer obliged to provide new scientific evidence, in order to enforce the ''Safeguard Clause'' (Directive 2001/18/EC, Article 23), which allows that *''Member State may provisionally restrict or prohibit the use and/or sale of that GMO as or in a product on its territory''*. • 19 EU Member States have filed *''demands for restriction of the geographical scope of a GMO application or authorisation''*[v]: Austria, Region of Wallonia (Belgium), Bulgaria, Croatia, Cyprus, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Slovenia, Northern Ireland, Wales and Scotland (United Kingdom) (see inset in Fig. 1)

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)
	Current review activities: • February 2012: European Food Safety Authority (EFSA) Panel on Genetically Modified Organisms (GMO) published a ''*Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis*'' (European Food Safety Authority, Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis 2012): ◯ ''*[. . .] similar hazards can be associated with cisgenic and conventionally bred plants, while novel hazards can be associated with intragenic and transgenic plants.*'' ◯ ''*The frequency of unintended changes may differ between breeding techniques and their occurrence cannot be predicted and needs to be assessed case by case.*'' • October 2012: European Food Safety Authority (EFSA) Panel on Genetically Modified Organisms (GMO) published a ''*Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function*'' (EFSA, 2012b) (European Food Safety Authority, Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nuclease with similar function 2012) • September 2014: publication of the opinion of the Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS) on ''*Synthetic Biology I – Definition*''.[w] • May 2015: publication of the opinion of the Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS) on ''*Synthetic Biology II – Risk assessment methodologies and safety aspects*''.[x] • December 2015: publication of the opinion of the Scientific Committee on Health and Environmental Risks (SCHER), Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), Scientific Committee on Consumer Safety (SCCS) on ''*Synthetic Biology III – Research priorities*''.[y] • September 2017: the European Commission Scientific Advisory Mechanism (SAM) issued a paper on New Breeding Techniques (NBT) (Scientific Advice Mechanism, 2017) • November 2018: the European Commission's Chief Scientific Advisors published statement on the regulation of gene editing[z] Socio-economic factors: • The market of the European Union comprises over 500 Million consumers • The EU seed market is worth 7 Billion Euros per year; it contributes to a strongly positive trade balance in the agro-sector • According to a representative from the European Commission, the EU approved GMOs every year, however, the marketing of these products was being heavily criticised

Table 2 (*Continued*)

Country	Details of the regulatory framework (review)
India	Regulation of GMOs and GE in India: • Overarching *1989 ''Rules for the manufacture, use, import, export and storage of hazardous microorganisms/genetically engineered organisms or cells''*[aa]: ◯ These rules cover the entire spectrum of activities relating to research, development and use of GMOs and their products including new gene technologies (such as genome editing) ◯ The rules define *'gene technology'* as *''the application of the gene technique called genetic engineering''* including *''self-cloning and deletion as well as cell hybridisation,''* where *'genetic engineering'* means *''the technique, by which heritable material, which does not usually occur or will not occur naturally in the organism or cell concerned, generated outside the organism or the cell is inserted into said cell or organism. It shall also mean the formation of new combinations of genetic material by incorporation of a cell into a host cell, where they occur naturally (self-cloning), as well as modification of an organism or in a cell by deletion and removal of parts of the heritable material.''* (Friedrichs, Takasu, et al., 2019) ◯ As per the applicable definition of ''Gene Technology'' and ''Genetic Engineering, all new technologies are to be regulated as per existing regulatory framework. ◯ The rule is implemented by three different agencies, divided into six statutory committees: (i) Recombinant DNA Advisory Committee (RDAC), (ii) Institutional Biosafety Committee (IBSC), (iii) Review Committee on Genetic Manipulation (RCGM), (iv) Genetic Engineering Appraisal Committee GEAC), (v) State Biotechnology Coordination Committee (SBCC), (vi) District Level Committee (DLC) • Food-specific *''Food Safety and Standards Act, 2006''*[bb]: ◯ The act provides the Food Safety and Standards Authority of India to regulate GM food, based on the following definition: ■ Definition: *'''genetically engineered of modified food' means food and food ingredients composed of or containing genetically modified or engineered organisms obtained through modern biotechnology, or food and food ingredients produced from but not containing genetically modified or engineered organisms obtained through modern biotechnology''* Current review activities: • It is still under examination of regulatory agencies whether all new technologies should be regulated as per existing regulatory framework; appropriate Guidelines and Standard Operating Procedures will be drafted. Socio-economic factors: • More than 85 crop species were currently under various stages of R&D in India, and three crop species had been approved or were awaiting approval: ◯ BT-cotton was the only crop that had been fully approved, ◯ BT-brinjal (egg plant) had been subjected to a moratorium, due to an adverse public reaction, in the middle of its approval process, and ◯ Genetically engineered mustard was awaiting approval. • The moratorium on the approval of BT-brinjal is considered a political issue; India's neighbour Bangladesh, meanwhile, is said to have approved the growing and commercialisation of the plant (Friedrichs, Takasu, et al., 2019).

Table 2 (*Continued*)

Adapted from Friedrichs, Takasu, et al. (2019).

[a] CODEX ALIMENTARIUS – International Food Standards: http://www.fao.org/fao-who-codexalimentarius/en/.

[b] Sanitary and Phytosanitary Measures: https://www.wto.org/english/tratop_e/sps_e/sps_e.htm.

[c] International Plant Protection Convention: https://www.ippc.int/en/.

[d] According to FAO, the ''*so-called Cartagena Protocol on Biosafety to the 1992 Convention on Biological Diversity (2000)* (Secretariat of the Convention on Biological Diversity 2000) *[...] does not refer to genetically modified organisms but rather, for reasons that are not explicit, to ''living modified organisms'' but it is clear that the two terms should be regarded as synonymous.*'' http://www.fao.org/3/Y4955E/y4955e03.htm.

[e] US: 2017 Update to the Coordinated Framework: https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/update-coordinated-framework-regulation-biotechnology.

[f] US: National Strategy for Modernizing the Regulatory System for Biotechnology Products: https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra/national-strategy-modernizing-regulatory-system.

[g] More information on the APHIS AIR process can be found here: https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated.

[h] US report ''2016: Gene Drives on the Horizon: Advancing Science, Navigating Uncertainty, and Aligning Research with Public Values'': https://www.nap.edu/catalog/23405/gene-drives-on-the-horizon-advancing-science-navigating-uncertainty-and.

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[n] Food Standards Australia and New Zealand (FSANZ): http://www.foodstandards.gov.au/Pages/default.aspx.

[o] FSANZ review (2017): http://www.foodstandards.gov.au/consumer/gmfood/Pages/Review-of-new-breeding-technologies-.aspx.

[p] Countries in the European Union (EU) (as of 29 June 2018): Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden and the UK. Countries in the European Economic Area (EEA) (as of 29 June 2018): Iceland, Liechtenstein and Norway.

[q] EU Directive and Regulations (quoted from: https://europa.eu/european-union/eu-law/legal-acts_en, accessed 18.03.19):

[•]An EU ''directive'' is ''*a legislative act that sets out a goal that all EU countries must achieve. However, it is up to the individual countries to devise their own laws on how to reach these goals.*''

- An EU ''regulation'' is ''*a binding legislative act. It must be applied in its entirety across the EU.*''

[r] Fact Sheet: Questions and Answers on EU's policies on GMOs: http://europa.eu/rapid/press-release_MEMO-15-4778_en.htm (accessed 18.03.19).

[s] Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC - Commission Declaration. http://data.europa.eu/eli/dir/2001/18/oj.

[t] Directive (EU) 2015/412 of the European Parliament and of the Council of 11 March 2015 amending Directive 2001/18/EC as regards the possibility for the Member States to restrict or prohibit the cultivation of genetically modified organisms (GMOs) in their territory (Text with EEA relevance): http://data.europa.eu/eli/dir/2015/412/oj.

[u] Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed (Text with EEA relevance): http://data.europa.eu/eli/reg/2003/1829/oj.

[v] List of EU Member States' demands for restriction of the geographical scope of a GMO application or authorisation: https://ec.europa.eu/food/plant/gmo/authorisation/cultivation/geographical_scope_en (accessed 18.03.19).

[w] SCHER, SCENIHR, SCCS Opinion on Synthetic Biology I: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_044.pdf.

[x] SCHER, SCENIHR, SCCS Opinion on Synthetic Biology II: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_048.pdf.

[y] SCHER, SCENIHR, SCCS Opinion on Synthetic Biology III: http://ec.europa.eu/health/scientific_committees/emerging/docs/scenihr_o_050.pdf.

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Conflicts of interest

The authors declare no conflicts of interest.

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[3] More information on the OECD's Co-operative Research Programme: Biological Resource Management for Sustainable Agricultural Systems can be found at http://www.oecd.org/agriculture/crp/about-the-co-operative-research-programme-crp.htm.

[4] More information on the US Department of Agriculture Foreign Agricultural Service (USDA-FAS) can be found at https://www.fas.usda.gov/.

[5] More information on the Journal of ''*Transgenic Research*'' of Springer International Publishing can be found at https://link.springer.com/journal/11248.