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Review

Future-Proofing EU Legislation for Genome-Edited Plants: Dutch Stakeholders' Views on Possible Ways Forward

Jan Pieter van der Berg *, Lianne M. S. Bouwman, Evy Battaglia and Gijs A. Kleter

Wageningen Food Safety Research, Wageningen University and Research, Akkermaalsbos 2, P.O. Box 230, NL-6700 AE Wageningen, The Netherlands; lianne.bouwman@wur.nl (L.M.S.B.); evy.battaglia@wur.nl (E.B.); gijs.kleter@wur.nl (G.A.K.)

* Correspondence: janpieter.vanderberg@wur.nl

Abstract: Genome editing is an emerging, new breeding technology with numerous potential applications in plant breeding. In Europe, genome editing is regarded, in legal terms, as a genetic modification technique, hence plants obtained using these methods fall under the legislation for genetically modified organisms (GMOs). Despite the opportunities that genome editing brings to the plant sector, it also poses challenges to the regulatory system. For example, the enforcement of labelling and traceability requirements for GM foods and feeds may be impossible for small genome edits that are indistinguishable from natural mutations. In order to discuss potential adaptations of EU legislation with stakeholders from the Dutch plant breeding sector, five different scenarios of future regulation of plants obtained by means of genome editing were elaborated. These scenarios were discussed in depth, along with the potential applications of genome editing in plant breeding, as well as challenges and opportunities. Stakeholders particularly indicated their preference for new, future-proof legislation in the long term, which will also include products of novel technologies. Finally, we discuss potential short-term amendments to current legislation, including the exemption of certain small mutations, that would make it align with regulation of genome edited plants in non-EU countries.

Keywords: CRISPR-Cas; genome editing; GMO regulation; plant breeding

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1. Introduction

Plant breeding aims to combine desirable characteristics in crop plants, for instance to increase yield, improve disease resistance or tolerance to heat. Historically, crop breeders relied on conventional breeding methods, such as crossing and backcrossing, to introduce beneficial characteristics. By also using marker assisted selection, plant breeders have more insight and understanding into the traits that are passed on to their novel cultivars.

With the development of genetic modification tools, plant breeders can introduce specific genetic sequences encoding desirable characteristics in their cultivars. In recent years, new breeding technologies, such as genome editing, have further expanded the plant breeding toolbox. These biotechnological tools may supplement conventional breeding strategies in the development of cultivars with desirable traits.

Policy makers are faced with diametrically opposed arguments in favor or against the utilization of new breeding technologies (NBTs) in plant breeding. On the one hand, for example, these tools may be used to improve food security, safety, and nutritional characteristics, while on the other, these tools may be seen as novel techniques of genetic modification for which the risks are not yet fully understood. In the EU for instance, regulatory approval and pre-market safety assessment are required for products resulting from these novel technologies according to the EU legislation on genetically modified organisms (GMOs).

Here, we present the current developments in modern plant biotechnology as well as the challenges and opportunities they offer, and implications for the plant breeding sector.

Furthermore, we report results from discussions with relevant stakeholders from the plant breeding sector on potential scenarios for the regulation of these modern technologies. These legislative scenarios describe how small genome edits may be regulated since certain genome editing processes result in small genetic alterations resembling natural genetic variation. Finally, potential changes to regulation of genome editing are presented, which may aid in alignment with other nations' regulation of genome edited plants.

2. Recent Developments in Utilization of Genome Editing Tools in Plant Breeding

Important developments in modern plant biotechnology have in recent years resulted in genome editing technologies that enable the targeted modification of genetic sequences. Genome editing technologies can be used to make modifications as small as single nucleotide alterations in pre-defined locations in the plant genome. The main genome editing techniques include zinc finger nuclease (ZFN), transcription activator-like effector nuclease (TALEN), clustered regularly interspaced short palindromic repeats (CRISPR) and CRISPR associated protein (Cas). Particularly CRISPR-Cas has proven a useful tool in the development of new crops.

Genome editing technologies are versatile tools that in many cases make use of nucleases (or site-directed nucleases (SDNs)), which all function in a similar way by introducing a double strand DNA break in a target region. After introduction of this DNA break, the host's DNA repair machinery will start mending the gap either by means of the non-homologous end joining (NHEJ) pathway or through homology directed repair (HDR) when a suitable template sequence is available. Genome editing tools can be used to introduce genetic alterations ranging from small indels (SDN-1), as small as a single base pair, resulting from NHEJ; targeted small alterations introduced by means of HDR using a DNA repair template (SDN-2); or larger transgenic sequences introduced by HDR (SDN-3) [1]. Moreover, genome editing can be used for the introduction of various valuable traits, such as increased stress tolerance or disease resistance, or for the improvement of quality and yields [2]. Utilization of CRISPR-Cas-based methods for crop improvement have so far yielded various modified plant species [3], such as herbicide-resistant rice [4], powdery mildew-resistant wheat [5], β-carotene-rich bananas [6] and rice [7], soybean with improved oil quality [8], and waxy corn with higher yield [9].

The emergence of NBTs, such as genome editing, is challenging the current regulatory frameworks that exist for new plants and varieties. In Europe, genome editing has been identified as a technique of genetic modification. In a ruling of the Court of Justice of the European Union (CJEU) in 2018 [10] it was clarified that organisms obtained by mutagenesis techniques, which includes genome editing, are GMOs. Plants created by means of genome editing must conform with the legislation for GMOs, regardless of the type of modification that is introduced (i.e., SDN-1, SDN-2, and SDN-3), since all these genome editing techniques have been developed after 2001, the year in which the current EU legislation was implemented. Following this ruling, the Council of the European Union requested the European Commission to perform a study on new genomic techniques. This study includes amongst others; the advancement in new genomic techniques, the risk assessment of agri-food crops developed using these techniques, as well as societal and ethical aspects of gene editing technologies [11].

Different strategies may be employed to regulate plant varieties resulting from genome editing, as can be seen when comparing the regulations worldwide. In some jurisdictions, certain edits without introduction of foreign DNA, i.e., SDN-1, are not considered to be GMO by law (Australia [12]), or are exempted from regulations (USDA [13]). In Canada, a product-based regulation is in place, that requires all plants with novel traits to be approved, regardless of the origin of the trait [14].

3. Genome Editing in the Plant Sector: Opportunities and Challenges

Utilization of genome editing in crop breeding innovation offers certain advantages for the development of novel crop plants with enhanced traits. Compared to conventional

genetic modification strategies and random mutagenesis (e.g., by means of chemical treatment or ionizing radiation), genome editing tends to be more efficient, precise, and may reduce development time [15]. Furthermore, it is estimated that genome editing can shorten plant breeding programs considerably, by up to four to six years depending on the crop [2]. Innovative plant breeding companies have embraced the utilization of genome editing for the production of enhanced crop plants, such as sulfonylurea herbicide-tolerant canola (Cibus, San Diego, CA, USA), cyst nematode-resistant rice (Evogene, Rehovot, Israel), and mildew-resistant wheat (Calyxt, Roseville, MN, USA).

The advantages offered by genome editing allow plant breeders the flexibility of introducing minor genetic changes in target genes comparable to induced random mutagenesis but without introducing additional random mutations elsewhere in the genome. Additionally, many plant traits are polygenic and influenced by more than one gene, meaning that multiple edits are required to alter the phenotype of a crop, which may be difficult to achieve through random mutagenesis. However, introduction of edits at multiple sites in the genome is achievable using genome editing, for instance by means of multiplex CRISPR technology [16]. Concerns raised by the application of genome editing technologies in food production may be alleviated when plant breeding companies introduce transparent and well-established risk assessment strategies in their breeding programmes. Such a strategy may benefit the plant breeding sector, especially in times of rapid development of biotechnological tools.

As mentioned above, genome-edited plant varieties are legally deemed GMOs in the EU and therefore require approval for market release and cultivation according to specific GMO regulations. This standpoint on genome-edited GMOs, including those with only minor genetic alterations (i.e., SDN-1 genome edits), influences many aspects of the plant breeding sector, such as the need to compile extensive safety dossiers as well as their competitiveness with companies in regions with less strict GMO regulations. Conversely, the current situation may also be seen as beneficial, for instance the current GMO legislation in the EU provides clear boundaries. Another advantage of current regulations is that they extend the segregation between GMO and non-GMO plant products to genome-edited and non-edited products, hence not putting the integrity of "GMO and genome-editing free" labelling at risk. This also upholds the freedom of choice for farmers not wanting to grow genome-edited products or feed them to their animals, and for consumers who are reluctant to buy any derived products. The current GMO regulation may also be in line with the current public opinion on GMOs [17,18]. However, public opinion on GMOs may vary significantly per EU member state and may shift over time. In addition, as the European Commission pointed out in their 2021 study on new genomic techniques, this legislation poses challenges for its implementation. Moreover, it has already required legal interpretation in order to clarify if and how this legislation addresses new genomic techniques, which has proven contentious for stakeholders. For these and other reasons, the Commission explored in its report the question whether an update of legislation was needed [11].

Besides challenges for plant breeders, strict regulation of genome-edited crops also poses issues for authorities. As part of the application for placing a GMO on the market, the applicant is required to submit a specific detection and identification method for the GMO. This should also be required for genome-edited plant varieties, since organisms obtained by genome editing techniques are regarded as GMOs. Current market control strategies for GMO products rely on so-called event-specific detection methods, which can be used to detect and identify unique DNA sequences at the junction where foreign DNA is integrated into the plant's genome [19]. In specific cases, genome-edited plants may carry integrated foreign genetic material introduced by means of SDN-3 type edits, which is distinguishable from native DNA and therefore detectable. Genome editing is frequently used, however, to introduce small genetic changes that are indistinguishable from natural mutations. These small genome edits can be detected using current detection methods, such as qPCR or DNA sequencing but it will be impossible to unequivocally prove that these have resulted

from the use of genome editing technologies instead of other breeding practices. A recent study on the detection of genome-edited plants claimed that an introduced genome edit can be detected using PCR-based detection methods [20]. However, in a response to this study the European Network for GMO Laboratories (ENGL) concluded that this analytical method cannot be used to distinguish between natural mutations or mutations resulting from genome editing [21] Therefore, as mentioned by the ENGL in 2019, traceability of genome-edited plant products lacking a unique DNA signature will not be possible [22].

4. Potential Scenarios for Regulation of Modern Biotechnology

As mentioned above, under the current legislative situation in the EU, genome-edited crops and products of other new breeding technologies are regarded as GMOs based on the technique used to create them, even though any introduced small genome edits may be indistinguishable from natural small mutations. The current regulation of genome editing technologies and potential changes to legislation were discussed with relevant stakeholders.

A total of 13 stakeholders from the Dutch plant breeding sector, representing academia (1/13), interest groups from the sector (2/13) and plant breeding companies (10/13), participated in our workshops on the challenges and opportunities of genome editing techniques, as well as the current regulation of the application of these novel technologies. Five different potential legislative scenarios concerning GMO regulation and how to regulate products from genome editing were drawn up and discussed during these workshops. These five legislative scenarios are as follows:

1. Current EU situation

The current EU GMO regulations are retained, meaning that all genome-edited organisms (SDN-1, SDN-2, and SDN-3 edits) are regulated as GMOs. Pre-market approval is required according to Directive 2001/18/EC for the deliberate release of GMOs into the environment, such as for cultivation. Placing on the market of GMOs and derived products as foods or feeds is defined in Regulation (EC) 1829/2003, any GM products also require labelling as stated in Regulation (EC) 1830/2003.

2. Exemptions for small genome edits

The current GMO regulations are retained, as in scenario 1; however, small genome edits are exempt from regulation. Included in the exemption are SDN-1 edits, resulting from DNA repair following NHEJ, and SDN-2 edits resulting from DNA repair using a template DNA sequence. These SDN-1 and SDN-2 type edits are treated the same way as random mutagenesis. Products containing SDN-3 edits require approval according to the EU GMO regulations in this scenario.

3. A product-based approach

Novel organisms, including GMOs, require regulatory approval based on the novelty of introduced traits and associated risk characteristics. Organisms with novel genetic alterations, without a history of safe use or which pose potential risks to health or environment must be assessed for their safety. This would also include traits conferred by novel genome edits, be it SDN-1, SDN-2, or SDN-3 type edits. Applicants will be able to consult with authorities whether their product is novel or not and if so, a safety evaluation dossier will have to be submitted for pre-market approval.

4. Altered GMO definition

The legal definition of what constitutes a GMO, as stated in Directive 2001/18/EC, is altered to exclude certain genome-edited organisms that have been created without the introduction of foreign DNA (e.g., vectors, repair templates). This would exclude SDN-1 type genome edits, that were created without the introduction of DNA constructs (for instance by introduction of CRISPR-Cas9 ribonucleoprotein complex). Applicants may consult with authorities whether their product is a GMO and if so, a pre-market approval is required under current EU GMO legislation.

5. Altered risk assessment requirements

Due to the high precision of genome editing technologies the guidance for risk assessment is altered and the current EU GMO regulation is retained. Amendments are introduced in the risk assessment guidance, whereby requirements for the more precise SDN-1, SDN-2 and SDN-3 edited organisms are reduced. Data requirements may, for instance, be limited to molecular characterization, bioinformatics, and phenotype analysis.

A number of these scenarios reflect current regulatory systems in place globally. The Canadian regulation for novel organisms, food, and feed follows a product-based approach, similar to scenario 3, where novel products are evaluated based on the novelty of the product [23]. Furthermore, scenario 4 is comparable to the legislation currently in place in Australia where a modified organism in which the genetic alteration did not involve the introduction of foreign genetic material is not regarded a GMO [24].

Following a short introduction on these potential scenarios, participants were asked to rank the scenarios from most (rank 1) to least (rank 5) preferred (Table 1). Results from the rankings were used to calculate the average score per scenario, which resulted in the final ranking in Table 1. Participants were asked to explain their rankings, leading to further discussions on these scenarios. Participants' views on the scenarios are further elaborated below.

Table 1. Participants' ranking of potential legislative scenarios.

Rank	Scenario
No. 1–Most preferred	Scenario 2 (exemptions for small gene edits), average rank score 1.4, (ranked No. 1 by 7 out of 13 participants)
No. 2	Scenario 4 (altered genetically modified organism (GMO) definitions), average rank score 2.4, (ranked No. 2 by 7 out of 13 participants)
No. 3	Scenario 5 (altered risk assessment requirements), average rank score 3.8
No. 4	Scenario 3 (a product-based approach), average rank score 4.2
No. 5–Least preferred	Scenario 1 (current EU situation), average rank score 4.7, (ranked No. 5 by 5 out of 13 participants)

5. Dutch Stakeholders' Views on Potential Legislative Scenarios

Stakeholders were asked for their opinion on the five scenarios mentioned above and their preferences were discussed as well as potential changes to these regulatory scenarios. A summary of benefits and concerns for each scenario raised by relevant stakeholders is presented in Table 2. Participants unanimously agreed with the fact that any changes to legislation should provide clear guidelines, should be based on scientific evidence, and should consider the benefits of genome editing. All stakeholders preferred a change from the current GMO regulation. Exemption of small gene edits from GMO regulation (scenario 2, ranked most favorite by 7 out of 13 participants) or changing of the GMO definition (scenario 4, ranked second most favorite by 7 out of 13 participants) were preferred as these were regarded to be feasible solutions that can be implemented in a relatively fast manner. Both the product-based approach (scenario 3) and decreased risk assessment requirements scenarios (scenario 5) raised several concerns, about uncertainty ("what is regarded as novel?", "will products be accepted when a safety dossier with a reduced amount of data is submitted?"), the fear for lengthy and costly approval procedures, as well as the fact that labelling may still be required. However, positive remarks were also voiced about these two scenarios: One stakeholder preferred the flexibility and case-by-case nature of a product-based approach and two stakeholders favored altered risk assessment requirements since it means that adaptation of legislation is not required. The current EU GMO legislation (scenario 1, ranked least favorite by 5 out of 13 participants) was least popular amongst stakeholders because it hinders the competitive position of European companies and is not a feasible situation in the long term since products from genome editing cannot be regulated according to current EU GMO regulation. Stakeholders did

appreciate the clarity of current EU regulation, particularly the clear boundaries that are defined for what constitutes a GMO and what not.

Table 2. Relevant stakeholders' remarks to different regulatory scenarios.

Scenario	Benefits	Concerns
1—Current EU situation	1. Clarity of the legislation, clear boundaries are defined in current legislation on what constitutes a GMO and what does not	1. Impact on global competitive position 2. Not feasible for the long term 3. Risk of utilization of new breeding technology (NBT)-derived plants from outside the EU, which are impossible to detect
2—Exemptions for small gene edits	1. Fast and feasible solution to implement 2. Clear distinction between host's and foreign DNA	1. May not be future-proof, other changes may be required, such as a multi-tiered approach to cover NBTs and other novel technologies in legislation 2. Adding many exemptions to legislation may harm social acceptance
3—A product-based approach	1. Use of this approach together with Convention on Biological Diversity (CBD) definition of living modified organisms may offer flexibility	1. Uncertainty about what is deemed "novel" 2. Fear of a lengthy and costly approval procedure due to uncertainty 3. Uncertainty whether products from conventional breeding with novel traits require approval
4—Altered GMO definition	1. Fast and feasible solution	1. May negatively impact social acceptance 2. Unclear whether site-directed nuclease (SDN)-2-type edits are also included in this scenario
5—Altered risk assessment requirements	1. Since legislation does not need to be adapted, implementation can be quick	1. Difficult to predict whether products will be accepted

Taken together, relevant stakeholders preferred a relatively quick adaptation of current regulation, either through the exemption of certain genome edits from current regulation or by changes to the definition of what constitutes a GMO. However, it was mentioned that these options can be regarded as "quick fixes", and that they may not be future-proof. With such changes, there is still a need to prepare legislation for future developments in biotechnology. Furthermore, stakeholders stress that care should be taken not to introduce too many exemptions to regulation as these may be negatively perceived as workarounds to the regulatory system, and that exemptions should be science-based.

6. Potential Changes in Regulation

The current regulatory framework for GMOs in the EU follows a process-driven approach. Within this framework it is assessed whether a modification has been introduced in an "unnatural" way. Organisms harbouring such unnatural modifications are regulated. Certain random mutagenesis techniques, such as mutagenesis by means of ionizing radiation, are considered to be GMO techniques according to the GMO Directive but are exempt from regulation owing to their history of safe use. The CJEUs ruling in Case C-528/16 on the scope of the GMO Directive explicitly precludes new mutagenesis methods from the list of exemptions, as only techniques with a substantial application and a long history safe use may be exempted from GMO regulation. The ruling states that products resulting from

new mutagenesis may be produced faster and in larger quantities than products resulting from conventional methods of random mutagenesis techniques with a history of safe use. In the view of the CJEU, the precautionary principle still applies to these new techniques of mutagenesis which have largely been developed since the enactment of current GMO legislation (Directive 2001/18/EC), and that therefore organisms produced using new methods of mutagenesis cannot be excluded from the scope of the GMO Directive. Moreover, the CJEU argues that the same types of modification could be achieved with these new mutagenesis methods as through transgenesis, and that therefore the same protection should be afforded against associated risks to human health and the environment [10].

Based on the information at hand about genome editing and associated issues concerning detection and traceability [22], changes to current regulation are required to provide clarity for developers wishing to use these novel biotechnological tools. Potential amendments to current regulation could entail minor adaptations, for instance the addition of SDN-1 type genome edits to the list of exemptions to GMO regulations. In discussions with relevant stakeholders this example scenario was preferred, especially when SDN-2 type gene edits were also included in the list of exemptions.

Any new amendments to regulation should preferably gather broad support from different sections of society. Recent surveys on food safety and food-related risks in the EU have shown that a significant number of European citizens are concerned about genetically modified ingredients in food products. A limited number of respondents named genome editing as primary food risk (4% EU-wide) in the latest Eurobarometer survey, but this may be due to unfamiliarity with genome editing technology. Only 21% of respondents confirmed that they heard about genome editing compared to 60% for genetically modified ingredients [18].

Based on the concerns regarding the application of biotechnological tools for the enhancement of crops there is a need to include the public in the decision-making for the regulation of NBTs. In a recent report on the ethics of genome editing, the European Group on Ethics in Science and New Technologies (EGE) considers and discusses the application of genome editing through an ethical analysis [25]. In their analysis the EGE states the benefits of genome editing technologies, in particular CRISPR-based methods, but also focuses on issues such as the impact of genome editing on biodiversity and food security.

7. Discussion

In our workshops with stakeholders from the plant breeding sector, preferences for legislative scenarios were discussed. The scenario where SDN-1 and SDN-2 type genome edits are exempt from GMO legislation, was preferred the most as this amendment can be quickly applied to current regulation. Such an adaptation of legislation would, at least for now, make it internationally more aligned with other jurisdictions such as the United States, Australia, Japan, and Argentina.

For competent authorities, which enforce legislation, currently it is possible to detect known SDN-1 and SDN-2-type DNA alterations, however this does not confirm whether these are the result of genome editing. Furthermore, it will be difficult without prior knowledge of the genetic alterations to detect the presence of unauthorized genome-edited products in imported food or feed. Exemptions from regulation for SDN-1 and SDN-2 type genome edits, as these are similar to mutations introduced by conventional breeding practices, would alleviate the need to submit a detection method to comply with the current regulatory system. At the time of this writing, no reliable detection method exists that can provide unequivocal evidence that can demonstrate that a product is the result of genome editing technologies. It can also be argued on these grounds that, for example, plants produced from SDN-1 applications do not pose higher risks than those from conventional breeding (e.g., [26]). Nonetheless, the CJEU clarified that exempting these newer techniques from the scope of GMO regulations would depart from the precautionary principle underlying the current legislation of GMOs within the EU,

since only those organisms are eligible that have been obtained with techniques with a long record of conventional application and safety.

Recently, a study on the status of genome editing under EU law, ordered by the Council of the European Union, was published [11]. This report focused on genome editing in general, where besides agri-food, medical and industrial applications were also evaluated. It concluded that the current regulations are "not fit for purpose", for genome editing, and that they should be changed in such a way that recent scientific insight and technological developments are considered. The report concludes that a future study is needed to address the question if and how the legislation should be updated, to make it both future proof and resilient [11].

a. The conclusions presented in the European Commission study were largely similar to our findings regarding the situation under EU law. For example, the challenges for detection, as we discuss under heading 3, are also recognized in the European Commission study. Concerns regarding the current EU legislation are also acknowledged, such as the competitive disadvantage for the sector, the ill-suitedness of current GMO regulation for the future, as well as missed opportunities of not using new technologies.
b. An important difference between our study and the recent report is that in our workshop, there were only relevant stakeholders from the plant breeding sector, mainly scientists from plant breeding companies as well as from academia, while in the European Commission study also views from member states and *inter alia* environmental NGOs were taken along. Differences on safety of new genomic techniques and labeling were touched upon in our stakeholders' discussion but are addressed more into detail in the European Commission study [11].
c. The discrepancy between the stakeholders' perspective on a suitable regulatory scenario on the one hand, and that of the general public on the other hand (such as may be derived from the Eurobarometer) is more pronounced in the European Commission study. Dialogue may be able to bridge the gap to some extent, in helping to increase understanding and awareness with regards to new biotechnologies. However, chances of reconciling opposing views on genome editing may be limited if the history and development of the GMO debate are an indication for this discussion.
d. A suggestion for the way regulations could be altered is not given in the European Commission study, although it is recommended to look for ways that would future-proof legislation in a way that considers benefits as well as concerns.
e. Narrowing the discussion to one topic at a time may enable targeted discussions and political decisions. In practice, this may mean separating the discussion on application of genome editing in crop plants from discussions on medical applications and applications in micro-organisms and animals. Divergences in stakeholders' views from the animal and microbial biotechnology sectors from those of their counterparts from the plant breeding sector, for example, also became evident in the discussions we had during workshops with these groups (no details provided here).
f. Finally, more international alignment of the legislation on genome editing of plants is something to strive for in the long run. Due to the various regulations in countries worldwide, differing either in detail or in essence of the legislation, global harmonization is still out of reach [27].

8. Concluding Remarks

In the EU, novel crops developed using genome editing technologies are regarded as GMOs, irrespective of the type of introduced edit (i.e., SDN-1, SDN-2, or SDN-3). As is also noted in the recent study on new genomic techniques by the European Commission, new breeding technologies, including genome editing, may contribute to sustainability in the European agri-food sector, and that future-proofing of regulations should consider such benefits as well as concerns, such as impacts on organic farming practices.

In our discussions with stakeholders from the Dutch plant breeding sector a scenario where SDN-1 and SDN-2 type genome edits are exempt from GMO regulation was preferred. This would also align with the regulatory route taken by various international trading partners of the EU, and hence help to prevent undue trade disruption through diverging legal requirements and restrictions between exporting nations and the EU as a large importer of agri-food commodities. While the stakeholders consider this the best short-term adaptation to legislation on genome editing techniques, they stress that other changes may be needed in the longer term to render legislation future-proof. Such legislation should adequately deal with any other new technology and should preferably be aligned with other nations' regulations on genome-edited agri-food products.

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References

1. EFSA Panel on Genetically modified organisms (GMO). Scientific Opinion Addressing the Safety Assessment of Plants Developed Using Zinc Finger Nuclease 3 and Other Site-Directed Nucleases with Similar Function. *EFSA J.* **2012**, *10*, 2943. [CrossRef]
2. Chen, K.; Wang, Y.; Zhang, R.; Zhang, H.; Gao, C. CRISPR/Cas Genome Editing and Precision Plant Breeding in Agriculture. *Annu. Rev. Plant Biol.* **2019**, *70*, 667–697. [CrossRef]
3. Parisi, C.; Rodriguez Cerezo, E. *Current and Future Market Applications of New Genomic Techniques*; European Commission: Luxembourg, 2021. [CrossRef]
4. Sun, Y.; Zhang, X.; Wu, C.; He, Y.; Ma, Y.; Hou, H.; Guo, X.; Du, W.; Zhao, Y.; Xia, L. Engineering Herbicide-Resistant Rice Plants through CRISPR/Cas9-Mediated Homologous Recombination of Acetolactate Synthase. *Mol. Plant* **2016**, *9*, 628–631. [CrossRef] [PubMed]
5. Wang, Y.; Cheng, X.; Shan, Q.; Zhang, Y.; Liu, J.; Gao, C.; Qiu, J.L. Simultaneous Editing of Three Homoeoalleles in Hexaploid Bread Wheat Confers Heritable Resistance to Powdery Mildew. *Nat. Biotechnol.* **2014**, *32*, 947–951. [CrossRef]
6. Kaur, N.; Alok, A.; Kumar, P.; Kaur, N.; Awasthi, P.; Chaturvedi, S.; Pandey, P.; Pandey, A.; Pandey, A.K.; Tiwari, S. CRISPR/Cas9 directed editing of lycopene epsilon-cyclase modulates metabolic flux for β-carotene biosynthesis in banana fruit. *Metab. Eng.* **2020**, *59*, 76–86. [CrossRef]
7. Dong, O.X.; Yu, S.; Jain, R.; Zhang, N.; Duong, P.Q.; Butler, C.; Li, Y.; Lipzen, A.; Martin, J.A.; Barry, K.W.; et al. Marker-Free Carotenoid-Enriched Rice Generated through Targeted Gene Insertion Using CRISPR-Cas9. *Nat. Commun.* **2020**, *11*, 1178. [CrossRef] [PubMed]
8. Haun, W.; Coffman, A.; Clasen, B.M.; Demorest, Z.L.; Lowy, A.; Ray, E.; Retterath, A.; Stoddard, T.; Juillerat, A.; Cedrone, F.; et al. Improved Soybean Oil Quality by Targeted Mutagenesis of the Fatty Acid Desaturase 2 Gene Family. *Plant Biotechnol. J.* **2014**, *12*, 934–940. [CrossRef] [PubMed]
9. Gao, H.; Gadlage, M.J.; Lafitte, H.R.; Lenderts, B.; Yang, M.; Schroder, M.; Farrell, J.; Snopek, K.; Peterson, D.; Feigenbutz, L.; et al. Superior Field Performance of Waxy Corn Engineered Using CRISPR–Cas9. *Nat. Biotechnol.* **2020**, *38*, 579–581. [CrossRef] [PubMed]
10. Court of Justice of the European Union Judgment of 25 July 2018—Case C-528/16, ECLI:EU:C:2018:583. Available online: https://e-justice.europa.eu/ecli/ECLI:EU:C:2018:583 (accessed on 6 February 2020).
11. European Commission. *European Commission Study on the Status of New Genomic Techniques under Union Law and in Light of the Court of Justice Ruling in Case C-528/16*; European Commission: Brussels, Belgium, 2021.

12. OGTR Overview of Amendments to the Gene Technology Regulations. 2001. Available online: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/content/23A002A6AC8A4908CA258478000D2031/$File/OverviewofamendmentstotheGeneTechnology-Regulations2001.pdf (accessed on 31 March 2021).
13. USDA APHIS Movement of Certain Genetically Engineered Organisms. *Fed. Regist.* **2020**, *85*, 29790–29838.
14. CFIA Gene Editing Techniques. Available online: https://inspection.canada.ca/plant-varieties/plants-with-novel-traits/gene-editing-techniques/eng/1541800629219/1541800629556 (accessed on 20 May 2021).
15. Lyzenga, W.J.; Pozniak, C.J.; Kagale, S. Advanced Domestication: Harnessing the Precision of Gene Editing in Crop Breeding. *Plant Biotechnol. J.* **2021**, *19*, pbi.13576. [CrossRef] [PubMed]
16. McCarty, N.S.; Graham, A.E.; Studená, L.; Ledesma-Amaro, R. Multiplexed CRISPR Technologies for Gene Editing and Transcriptional Regulation. *Nat. Commun.* **2020**, *11*, 1281. [CrossRef] [PubMed]
17. European Commission. *TNS Opinion & Social Special Eurobarometer 354 Food-Related Risks*; Publications Office of the European Union: Luxembourg, 2010.
18. European Commission. *Kantar Special Eurobarometer Wave EB91.3—Food Safety in the EU*; Publications Office of the European Union: Luxembourg, 2019.
19. Grohmann, L.; Keilwagen, J.; Duensing, N.; Dagand, E.; Hartung, F.; Wilhelm, R.; Bendiek, J.; Sprink, T. Detection and Identification of Genome Editing in Plants: Challenges and Opportunities. *Front. Plant Sci.* **2019**, *10*, 236. [CrossRef] [PubMed]
20. Chhalliyil, P.; Ilves, H.; Kazakov, S.A.; Howard, S.J.; Johnston, B.H.; Fagan, J. A Real-Time Quantitative PCR Method Specific for Detection and Quantification of the First Commercialized Genome-Edited Plant. *Foods* **2020**, *9*, 1245. [CrossRef]
21. ENGL. *ENGL Evaluation of the Scientific Publication "A Real-Time Quantitative PCR Method Specific for Detection and Quantification of the First Commercialized Genome-Edited Plant"*; European Network of GMO Laboratories (ENGL): Brussels, Belgium, 2020.
22. ENGL. *Detection of Food and Feed Plant Products Obtained by New Mutagenesis Techniques*; European Network of GMO Laboratories (ENGL): Ispra, Italy, 2019.
23. Health Canada Guidelines for the Safety Assessment of Novel Foods. Available online: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/hpfb-dgpsa/pdf/gmf-agm/guidelines-lignesdirectrices-eng.pdf (accessed on 13 April 2021).
24. OGTR Technical Review of the Gene Technology Regulations 2001, 2019 Amendments to the Gene Technology Regulations. 2001. Available online: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewregulations-1 (accessed on 29 July 2019).
25. European Commission. *EGE opinion on the Ethics of Genome Editing*; Publications Office of the European Union: Luxembourg, 2021. [CrossRef]
26. EFSA Overview of EFSA and European National Authorities' Scientific Opinions on the Risk Assessment of Plants Developed through New Genomic Techniques. *EFSA J.* **2021**, *19*, 6314. [CrossRef]
27. Menz, J.; Modrzejewski, D.; Hartung, F.; Wilhelm, R.; Sprink, T. Genome Edited Crops Touch the Market: A View on the Global Development and Regulatory Environment. *Front. Plant Sci.* **2020**, *11*, 586027. [CrossRef]