Policy scenarios for new genomic techniques

Analysis of strengths, weaknesses, opportunities and threats of four policy scenarios for new genomic techniques within the regulatory framework for genetic modification

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This research has been carried out by Wageningen Food Safety Research, institute within the legal entity Wageningen Research Foundation subsidised by the Dutch Ministry of Agriculture, Nature, and Food Quality (project number BO-42-112-001).

Wageningen, June 2022

CONFIDENTIAL

WFSR Report 2022.514

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, 2022. *Policy scenarios for new genomic techniques; Analysis of strengths, weaknesses, opportunities and threats of four policy scenarios for new genomic techniques within the regulatory framework for genetic modification.* Wageningen, Wageningen Food Safety Research, Confidential WFSR Report 2022.514. 82 pp.; 2 fig.; 6 tab.; 34 ref.

Project number: 1287364901
BAS-code: BO-42-112-001
Project title: Ontwikkeling methodiek voor product-gebaseerde borging voedselveiligheid
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www.wur.eu/food-safety-research. WFSR is part of Wageningen University & Research.

Confidential WFSR report 2022.514

Distribution list:

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Preface

The **aim** of this report is to give a clear overview of the Strengths, Weaknesses, Opportunities and Threats for the policy scenarios for the regulation of genome editing techniques in food and feed production.

This overview is focused on three major application fields: plant breeding, animal breeding (livestock farming & fisheries) and industrial microbiology (for food & feed purposes).

Four policy scenarios are presented:

- Scenario A: Current EU legislation is retained: a process-based scenario.
- Scenario B: Current EU legislation with an adjustment of risk assessment for genome edited organisms.
- Scenario C: Distinction in type of edits: some types of edits will be excluded from legislation, but definition remains process-based.
- Scenario D: Product-based scenario, (precautionary principle will not be retained).

The **scope** is genome editing techniques and other DNA sequence altering techniques, such as CRISPR-Cas and other Site-Directed Nuclease technologies, and does NOT include RNA altering or epigenomic techniques.

The focus is limited to the application of these techniques for food & feed purposes and does not include medical and pharmaceutical applications.
Furthermore the report focusses on (adjustment of) EU legislation.

Summary

New genomic techniques (NGTs) enable the targeted modification of DNA. NGTs fall under the regulations for genetically modified organisms (GMOs) in the European Union. However, this regulatory framework is considered not fit for purpose according to a recent report of the European Commission. Moreover, it differs considerably from the approaches taken in some other jurisdictions.
This report discusses four scenarios for regulation of GMOs and NGTs, and lists their important strengths (advantages), weaknesses (disadvantages), opportunities (positive implications this scenario brings) and threats (negative implications this scenario brings).

The analysis focused on the plant breeding sector, the animal breeding sector and industrial microbiology. A series of interviews with experts in GMO regulation from various countries worldwide (Argentina, Australia, Canada, Japan, South-Africa, USA) form the basis of this analysis, combined with results from interviews and workshops with stakeholders in the Netherlands and scientific literature.

Scenario A: Current EU situation	
Strengths / Advantages	**Opportunities / Positive implications**
• Clear GMO definition • In line with public opinion • Alignment with precautionary principle	• Clear positioning of organic and GMO-free products
Weaknesses / Disadvantages	**Threats / Negative implications**
• Difficult: detection small genome edits • Missing definitions (e.g. mutagenesis) • Difference GMO definition elsewhere in the world • Not science-based • Discrepancy: random mutations vs precise genome editing techniques • Not fit for future genetic engineering developments • No steps taken to take away uncertainties (precautionary principle)	• Impact on innovation • Impact on competitiveness EU • Revert to CJEU for each new technique • Accidental use of NGT products • Barriers to international trade • Labelling duty not enforceable • Circumvention of legislation
Scenario B: Current EU regulation with adjusted risk assessment (i.e. less safety data required) for organisms obtained by genome editing	
Strengths / Advantages	**Opportunities / Positive implications**
• Clear GMO definition • Alignment with precautionary principle • No need for fundamental adaptations to current regulation • Risk-based analysis possible • Safety of genome editing techniques can be verified	• Shorter safety dossiers (shorter approval period, lower financial burden) • Enables use of gene editing techniques to some extent
Weaknesses / Disadvantages	**Threats / Negative implications**
• Difficult: detection small genome edits • Missing definitions (e.g. mutagenesis) • Difference GMO definition elsewhere in the world small genome edits	• Impact on innovation • Impact on competitiveness EU • Revert to CJEU for each new technique • Labelling duty not enforceable

Scenario C: Organisms with a small edit without introduction of DNA stretches are exempted from GMO legislation (i.e. SDN-1 or SDN-2 type edits)	
Strengths / Advantages	**Opportunities / Positive implications**
• Feasibility for enforcement: detection possible of foreign DNA • Fast implementation possible • Labelling duty enforceable	• Knowledge development in Europe, possibility to use gene editing techniques • Competitive situation of Europe
Weaknesses / Disadvantages	**Threats / Negative implications**
• Organisms with multiple (complex) mutations difficult to judge • Arbitrary definition of a small edit • "Perfect allele replacement" not exempted • Small mutations may have great consequences (particularly for animals)	• Regulation not future-proof • Potential negative public opinion due to addition of exemptions • Viability organic sector disadvantaged. • Other changes in the food system may receive less attention • Regulations (bans) on national level
Scenario D: Product-based regulation, whereby on a case-by-case basis will be decided whether an organism must be assessed for its safety. The characteristics of the organism determine this necessity, rather than the process used to obtain the organism	
Strengths / Advantages	**Opportunities / Positive implications**
• Pragmatic, case-by-case approach • Future proof regulation • Principle of equivalence: similar changes judged in a similar way	• Enables use of gene editing techniques for food production • Competitive position of European companies retained
Weaknesses / Disadvantages	**Threats / Negative implications**

• Unclear what will be deemed "novel"
• History of safe use:
  ○ Cut-off moment and interpretation
  ○ By GMOs not considered
	• Now exempt new varieties may require approval
	• Lengthy and costly approval procedures
	• Viability organic sector viability disadvantaged

The following points were considered most important for further discussion:

- The distinction between product versus process-based approaches is in practice no sharp contrast; international stakeholder interviews show that this is a mix in every country.
- A consultation procedure, such as in place in some form in various countries (in i.a. Argentina, Canada, Japan and USA) provides clarity to developers and enables authorities to be aware of important developments.
- Currently, it is mandatory to assess the safety of GMOs and to label consumer products with or from GMOs in the EU. Other approaches, such as no obligatory labelling (USA, Canada) or labelling except for gene-edited products with only small edits (Japan) can also be possible.
- The costs to compose a safety dossier are considerable for developers, but also the assessment of dossiers is a costly practice for countries. Both costs are positively influenced (reduced) by international harmonization of safety assessment requirements.
- History of safe use: it would be valuable to discuss if and when this might also be established for new technologies at some point after their introduction.
- The current discussion at the EU level focuses particularly on plants, yet implications for animal and microbial sectors are also relevant.
- Other considerations besides safety are also important, such as co-existence with organic agriculture, consumer acceptance, and innovation.

In conclusion, food safety can be guaranteed by all scenarios. From a detection and enforcement point of view, scenarios C and D ensure that these remain technically feasible for products that are not excluded from the scope of GMO regulations. The final decision on the best option for the EU, based on careful weighing of all technical and socio-economic aspects, rests with decision makers at the European community level.

Nederlandse samenvatting

Nieuwe genomische technieken (NGTs) maken het mogelijk om DNA gericht te modificeren. In de Europese Unie vallen deze NGTs onder de regelgeving voor genetisch gemodificeerde organismen (GGOs). Echter, dit regelgevingskader is niet geschikt bevonden voor het doel in een recent rapport van de Europese Commissie, en het verschilt aanzienlijk van de benadering voor NGTs die in bepaalde andere jurisdicties wordt genomen. Dit rapport bediscussieert vier scenario's voor de regelgeving voor GGOs en NGTs, en vat de belangrijkste sterktes (voordelen), zwaktes (nadelen), kansen (verwachte positieve implicaties) en bedreigingen (verwachte negatieve implicaties) voor deze vier scenario's.

De analyse focust zich op de plantenveredeling sector, de dieren sector en de industriële microbiologie. Een serie van interviews met experts in GGO regelgeving afkomstig uit verschillende landen wereldwijd (Argentinië, Australië, Canada, Japan, de Verenigde Staten, en Zuid-Afrika), zijn gebruikt voor deze analyses, in combinatie met (eerder uitgevoerde) interviews en workshops met Nederlandse stakeholders en de wetenschappelijke literatuur.

Scenario A: Huidige EU regelgeving	
Strengths / Voordelen	**Opportunities / Positieve implicaties**
• Heldere definitie GGO • In lijn met publieke opinie • Passend binnen voorzorgsprincipe	• Heldere positionering van organische en GGO-vrije (EU) producten
Weaknesses / Nadelen	**Threats / Negatieve implicaties**
• Moeilijk: detectie kleine genoom edits • Ontbrekende definities (bijv. mutagenese) • Verschil GMO definitie elders in de wereld • Niet gebaseerd op wetenschappelijke inzichten • Discrepantie: willekeurige mutaties vs precieze genome editing technieken • Niet toekomstbestendig • Geen actie om onzekerheden weg te nemen (voorzorgsprincipe)	• Impact innovatie • Impact concurrentievermogen EU • Gang naar Europees Hof bij iedere nieuwe techniek • Etiketteringsplicht niet handhaafbaar • Onbedoeld gebruik van NGTs • Barrières voor internationale handel • Ontwijking regelgeving
Scenario B: Huidige EU GGO regelgeving met aangepaste veiligheidsbeoordeling (dwz, minder veiligheidsdata standaard gevraagd) voor organismen verkregen met genome editing technieken	
Strengths / Voordelen	Opportunities / Positieve implicaties
• Heldere definitie GGO • Passend binnen voorzorgsprincipe • Geen noodzaak voor fundamentele aanpassing regelgeving • Risico-gebaseerde analyse mogelijk • Mogelijkheid veiligheid genome editing te verifiëren	• Beknoptere veiligheidsdossiers (kortere beoordeling, lagere financiële lasten) • Gebruik genome editing enigszins mogelijk
Weaknesses / Nadelen	**Threats / Negatieve implicaties**
• Moeilijk: detectie kleine genoom edits • Ontbrekende definities (bijv. mutagenese) • Verschil GGO definitie elders in de wereld	• Impact innovatie • Impact concurrentievermogen EU • Gang naar Europees Hof bij iedere nieuwe techniek • Etiketteringsplicht niet handhaafbaar

Scenario C: Organismen met een kleine edit waarbij geen DNA geïntroduceerd wordt (SDN-1 en SDN-2), zijn uitgesloten van GGO regelgeving	
Strengths / Voordelen	**Opportunities / Positieve implicaties**
• Handhaving: detectie mogelijk op basis van soortvreemd DNA • Snelle implementatie mogelijk • Etiketteringsplicht handhaafbaar	• Innovatie gestimuleerd, mogelijkheid nieuwe genome- edited organismen voor commercialisatie • Concurrentiepositie Europa
Weaknesses / Nadelen	**Threats / Negatieve implicaties**
• Arbitraire definitie "kleine edit" • Organismen met meerdere mutaties • "Perfecte allel vervanging" niet uitgezonderd • Kleine mutaties kunnen grote consequenties hebben (m.n. voor dieren)	• Regelgeving niet toekomstbestendig • Publieke opinie als gevolg van extra uitzonderingen • Organisch sector mogelijk bedreigd • Aandacht voor andere veranderingen voedselsysteem wordt kleiner • Regelgeving (verboden) op nationaal niveau
Scenario D: Productgebaseerde regulering, waarbij op een case-by-case manier wordt besloten of een organisme moet worden beoordeeld op veiligheid. De eigenschappen van het organisme besluiten of dit nodig is, en niet het proces dat gebruikt is om het organisme te verkrijgen.	
Strengths / Voordelen	**Opportunities / Positieve implicaties**
• Pragmatische, case-by-case aanpak, • Toekomstbestendig • Principe van equivalentie: vergelijkbare veranderingen worden op vergelijkbare manier beoordeeld	• Maakt gebruik genome editing technieken voor voedselproductie mogelijk • Concurrentiepositie van Europese bedrijven blijft behouden
Weaknesses / Nadelen	**Threats / Negatieve implicaties**

• Onduidelijk wat als "nieuw" bestempeld wordt
• Geschiedenis van veilig gebruik:
  ○ Cut-off moment en interpretatie
  ○ Bij GGOs niet beschouwd
	• Langdurige en dure goedkeuringsprocedures
	• Variëteiten die geen goedkeuring behoeven moeten ook beoordeeld worden
	• Organische sector mogelijk benadeeld

De onderstaande punten kwamen naar voren als meest relevant voor verdere discussie:

- Het onderscheid tussen een product- en een proces-gebaseerde aanpak in regelgeving is geen scherp contrast; de interviews met internationale stakeholders laten zien dat er in ieder land sprake is van een mix van beide aanpakken.
- Een consultatieprocedure, zoals bestaat in verschillende landen (o.a. in Argentinië, Canada, Japan en de Verenigde Staten) kan duidelijkheid verschaffen aan (product)ontwikkelaars en zorgt dat de autoriteiten op de hoogte zijn van belangrijke ontwikkelingen.
- Momenteel moeten GGOs in de EU zowel worden beoordeeld op hun veiligheid en moeten producten met of van GGOs verplicht als zodanig worden gelabeld. Andere aanpakken, zoals geen verplichte labelling (VS, Canada) of een verplichting tot labelling maar een uitzondering voor genome-edited producten met kleine edits (Japan) bestaan ook.
- De kosten voor een ontwikkelaar om een veiligheidsdossier op te stellen zijn aanzienlijk, maar ook de beoordelingsprocedure is een kostbare praktijk voor landen. Beide kostenposten worden positief beïnvloed (gereduceerd) door internationale harmonisatie van veiligheids-beoordelingsprocedures.
- Een geschiedenis van veilig gebruik: de discussie of dit ook bij nieuwe technieken kan worden vastgesteld een zekere tijd na hun introductie, zou van toegevoegde waarde zijn.
- De huidige discussie in de EU richt zich met name op het gebruik van NGTs in planten, maar implicaties voor het gebruik in dieren en micro-organismen zijn ook relevant.
- Ander overwegingen naast veiligheid zijn ook belangrijk, zoals de co-existentie met biologische landbouw, consumentenacceptatie en innovatie.

Concluderend, voedselveiligheid kan met alle scenario's gegarandeerd worden. Gezien vanuit een detectie- en handhavingsperspectief, bieden scenario's C en D de zekerheid dat deze haalbaar blijven voor de producten die niet vrijgesteld worden van GGO regelgeving. De uiteindelijke beslissing voor de beste optie voor de EU, waarbij alle socio-economische en technische aspecten mee worden genomen, ligt bij besluitvormers van de Europese gemeenschap.

1 Introduction

Selection and breeding of plants and animals for food and feed purposes is as old as agriculture itself. Nonetheless, only in the last century breeding has become more focused, due to increased knowledge on heredity and genetics and the availability of genome information. Mutagenesis breeding methods to introduce additional genetic variation in plants and micro-organisms have been used. In addition, transgenic techniques were developed, whereby genetic material could be randomly integrated in an unrelated organism.

Advances in molecular biology have rendered even more opportunities for breeding. Increased possibilities to sequence and study genetic material, and more knowledge of genes and their function makes that more targeted selection is possible as well.
New genomic techniques (NGTs), which are able to induce changes in DNA in a targeted manner, are considered to be promising tools for breeding and development in the agri-food sector.

Recently, the European Commission published a report (European Commision, 2021b) on the status of NGTs under EU law. These NGTs were defined as "techniques that are capable of altering the genetic material of an organism and that have emerged or have been mainly developed since 2001", as in 2001 the legislation as laid out in Directive 2001/18/EC for Genetically modified organisms (GMOs) came into force. The report concludes that the current GMO legislation is likely not fit for purpose for certain NGTs.

In order to provide additional background in the discussions on legislation, this policy supporting document explores various regulatory scenarios for genome editing techniques in food & feed production. The aim is to clearly summarize strengths, weaknesses, opportunities and threats for four policy scenarios, that find their basis in the current regulatory status of genome edited organisms worldwide.

The analysis focuses on three major fields in the agri-food sector: plant breeding, the animal sector: livestock farming & fisheries, and industrial microbiology for food & feed purposes. This report focusses on modifications in the DNA sequence, induced by site directed nucleases (SDNs). These modifications can be classified based on the type of DNA repair involved: double-stranded break repair without a template by non-homologues end joining (SDN1), or with a template by homology directed repair (SDN2 and 3), and the size of the modifications. See figure 1 for further details.

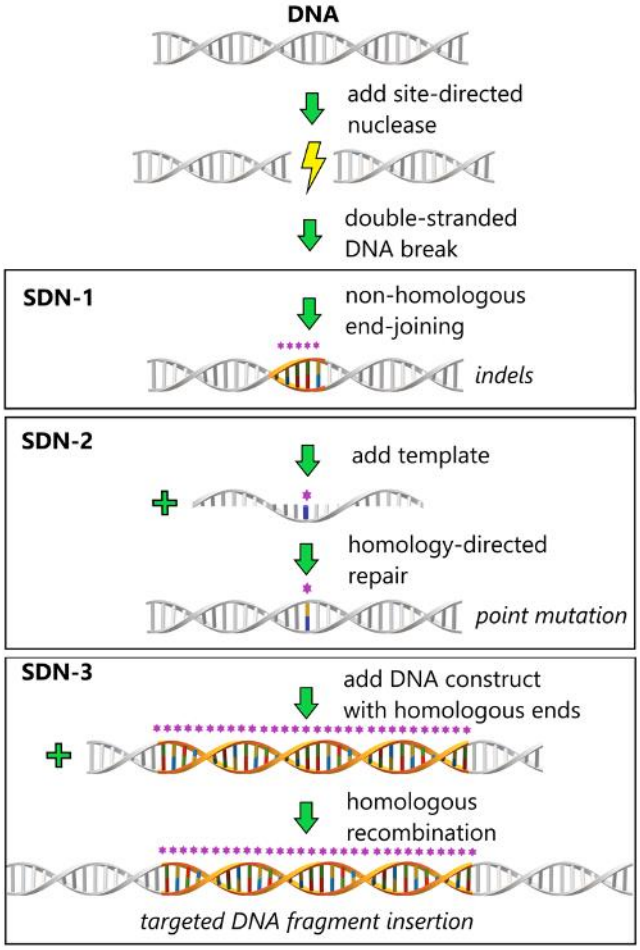

Figure 1 *Schematic overview of the types of SDN modifications, from: (Sturme, Van Der Berg, et al., 2022). The asterisks (*) signify nucleotides (in colour) that are not identical to the native host sequence (in grey) around the double-stranded break introduced by the SDN. Such non-identical nucleotides are introduced either through substitution or through insertion of nucleotides during the process of DNA break repair. SDN-1 applications can generate alterations of a single base pair up to a small number of base insertions/deletions (indels) without providing a donor DNA template, through non-homologous end-joining (NHEJ). SDN-2 applications can generate precise and small genetic modifications at the target site, ranging from point mutations to small indels, by means of a donor DNA template for homology-directed repair (HDR). SDN-3 applications can insert entire DNA cassettes into a target site, by providing a large donor DNA template of the desired gene, which leads to insertion by HDR or NHEJ.*

In the EC report and the supporting Joint Research Centre report, four categories of NGTs are distinguished (European Commision, 2021b; Parisi & Rodriguez Cerezo, 2021):

1. techniques that induce a double-stranded break in DNA (such as CRISPR Cas, ZFN, TALEN, and homing endonucleases);
2. techniques that make edits in DNA without breaking the DNA or with a single-strand DNA (such as oligonucleotide-directed mutagenesis (ODM), base editing and prime-editing);
3. techniques that lead to epigenomic alterations;
4. techniques altering RNA.

The focus of this report is on category 1 and 2: the NGTs that affect the DNA sequence.

2 Methodology

This report makes use of the results from the interviews with risk assessment experts/authorities and workshops with stakeholders from the biotechnology/breeding sector reported in WFSR report 2021.506. In addition, recent literature is taken into account on the regulatory status of genome-edited organisms worldwide and the experiences in practice. Most notably, a number of interviews were conducted digitally with experts worldwide on the process of updating legislation and their practical experiences. The original drafts of the analysis of strengths, weaknesses, threats and opportunities were used to draft questions for various experts from over the world in the field of risk assessment or (academic) experts focussing on genetic techniques. See Annex 1 for a list of the organisations of the interviewees.

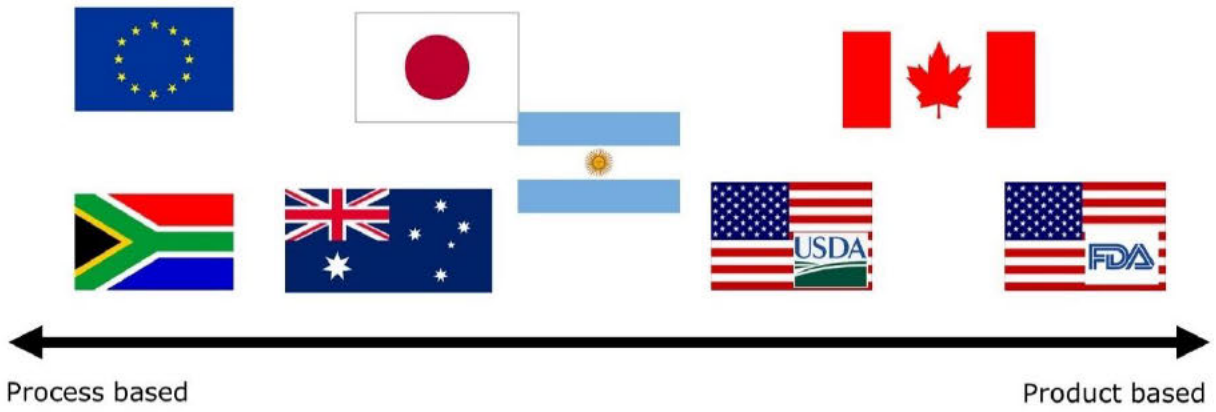

Figure 2 *Overview of the regulatory regimes for GMOs and genome edited organisms studied in this report, and the extent to which they may be characterized as process-based or product-based. From left to right: European Union, South-Africa, Australia, Japan, Argentina, USA (USDA), Canada, USA (FDA).*

Four scenarios

Four regulatory scenarios will be discussed, in Chapters 3 to 6. Table 1 provides a short overview of the scenarios, and each chapter starts with a description of the scenario.

The scenarios A (current EU), C (Small edit exemption) and D (product-based) are derived from the current regulatory status of genome edited organisms worldwide. Scenario B is a scenario drafted by the authors of this report, based on the European legislation. These scenarios have been previously discussed in workshops with Dutch stakeholders (WFSR report 2021.506; van der Berg et al., 2021).

Table 1 *Overview scenarios analysed.*

Scenario	Description of scenario	Short name	Chapter
A	Current, process-based EU legislation	Current EU	3
B	Current, process-based EU regulation with an adjustment of the risk assessment for GMOs, particularly those obtained by new genomic techniques	Adjusted Risk assessment	4
C	Distinction in type of edits: some types of edits will be excluded from GMO regulation, but the of GMOs definition remains process-based.	Small edit exemption	5
D	Product-based scenario, product-based regulation, whereby the necessity of a safety assessment is decided on a case-by-case, based on the characteristics of the end-product. The precautionary principle for new techniques is abandoned, only safety of end-product is relevant.	Product-based	6

Distinctions between strenghts, weaknesses, opportunities and threats

The main outcome of this report are the tables that analyse for four scenarios. In table 2, it is summarized how distinctions between the strengths or advantages, weaknesses or disadvantages, opportunities or positive implications and threats or negative implications are considered. Strengths and weaknesses: the focus is on factors inherent to the legislation for each of the described scenarios, in the present time. Opportunities and threats: here the scenario is placed in context, focusing on (potential) future developments.

Our analysis is similar to, but not the same as, a SWOT analysis as used in strategic marketing. In our approach, the analysis of opportunities and threats are based on expectations of positive and negative implications. In the standard SWOT approach the opportunities and threats are fact based, rather than assumption-based like in our analysis.

Table 2 *Explanation of the analysis tables, listing strengths, weaknesses, opportunities and threats.*

Strengths / Advantages	**Opportunities / Positive implications**
Positive factors inherent to legislation Focus on the present time	Placed in context: positive developments that are likely to occur Focus on future developments
Weaknesses / Disadvantages	**Threats / Negative implications**
Negative factors inherent to legislation Focus on the present time	Placed in context: negative developments that are likely to occur Focus on future developments

The tables summarize the most important strengths, weaknesses, opportunities, and threats, which are further explained and elaborated upon in the rest of the chapter.

In filling in the analysis tables, the following topics were considered in particular:

- Food safety
- Clarity of the regulation
  including answers to the following questions: Are the definitions unambiguous? Are the assessments procedures and their outcomes clear for applicants? (and why?)
- Enforceability of detection and traceability requirements imposed by the various policy options, and the technical detection possibilities
- Influence on innovation
- (Economic) position of European companies
- Public opinion & consumer acceptance

3 Scenario A: Current EU situation

3.1 Description of scenario A

In scenario A, the current EU GMO legislation would be retained without any amendment. This implies that all gene-edited organisms (SDN-1, SDN-2, and SDN-3 edits) are regulated as GMOs and require pre-market approval according to Directive 2001/18/EC for the deliberate release of GMOs into the environment, such as for cultivation, for placing on the market as foods and feeds (Regulation (EC) No.1829/2003), labelling and traceability (Regulation (EC) No.1830/2003), and contained use in case of genetically modified microorganisms (Directive 2009/41/EC).

The ruling of the Court of Justice of the European Union (C-528/16) clarified how the GMO definition has to be interpreted, and what is exempted from legislation. The Court clarified i.a. that organisms obtained by a method of mutagenesis are GMOs. In Article 3(1) in Directive 2001/18 and Annex IB, conventional mutagenesis techniques are exempt from GMO legislation. In Case C-528/16, the CJEU ruled that these exemptions only cover conventionally used mutagenesis techniques with a long safety record; thereby excluding NGTs from the exemption.

Table 3 *Analysis of scenario A: the current, process-based EU legislation.*

Scenario A: Current EU situation	
Strengths / Advantages	**Opportunities / Positive implications**
• Clear GMO definition • In line with public opinion • Alignment with precautionary principle	• Potential for clear positioning of organic and/or GMO-free products
Weaknesses / Disadvantages	**Threats / Negative implications**
• Difficult to establish detection strategies for small genome edits • Definitions of certain concepts are still missing (e.g., mutagenesis) • GMO definition not in line with those elsewhere • Not science-based • Not fit for future genetic engineering developments • Precautionary principle: no steps taken to take away uncertainties • Discrepancy between mutations generated by random mutagenesis (allowed) vs strict regulations for precise genome editing techniques	• Negative impact on innovation • Impact on competitiveness EU business • Revert to CJEU each time the applicability of the legislation to a new breeding innovation needs to be clarified • Accidental use of NGT products • Barriers to international trade • Labelling obligation not enforceable • Potentially easy to circumvent legislation

3.2 Analysis of scenario A

3.2.1 Strengths / Advantages

Clear GMO definition

In the workshops, a number of stakeholders have indicated that under the current EU legislation, it is clear which techniques, and thereby which organisms and products, are regulated (WFSR report 2021.506, page 51). Moreover, stakeholders from industry have indicated that there is no threat to the use of "conventional" mutagenesis techniques that are now exempt from regulations.
Strictly speaking, as clarified in case C-528/16, conventional mutagenesis techniques are also considered GMO technologies under the EU law but exempt from GMO regulation.

If regulations were to be changed, it would be uncertain how such conventional techniques are to be considered and whether they stay exempt from regulations. By maintaining the current legal situation, such uncertainties are not introduced.

Perceived to be in line with public opinion

The current GMO regulation was also considered to be in line with the perceived public opinion on GMOs as well as the public understanding of genetic techniques in general.

Biotechnology, in particular for agricultural and food related purposes, can be negatively perceived by the general public. This is the clearest for the attitudes towards GM foods, which have been assessed in European countries since the early 90s, showing that overall support for GM foods has declined over time (Gaskell et al., 2006, 2010).

Less information is available for public attitudes towards the novel genome editing techniques. Whilst in the Eurobarometer of 2019, 21% of the consumers were aware of the technique and 4% were concerned about it (EFSA, 2019).

Educating consumers on NGTs may be difficult and is hindered by the stigma of genetic modification that can affect attitudes towards gene editing (WFSR report 2021.506, page 53).

It was pointed out that the current EU situation is most in line with current public opinion (WFSR report 2021.506, page 56). Even though the novel breeding techniques have been introduced, the framings and questions from the public do not seem to have changed (WFSR report 2021.506, page 57).

Consumers (in Australia) tend to have a very different view towards conventional techniques and genetic techniques including NGTs. When techniques are discussed in detail, consumers have a more positive attitude towards changing existing genetic material than towards introducing genes (Interview Australia, Annex 1.2).

Alignment with the precautionary principle

The precautionary principle exists in European law to protect human and animal health and the environment against unknown risks. It is included in recital 8 of Directive 2001/18/EC: "the precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it". In addition, the precautionary principle was also an important factor in the judgment of the European Court of Justice in case C-528/16, which the court considered to be relevant for the new techniques of mutagenesis.

3.2.2 Weaknesses / Disadvantages

Difficult to establish detection strategies for small genome edits

One of the major problems signalled for the current EU legislation is the difficulty in establishing reliable detection methods, particularly for small edits. This argument has been brought forward by academic and company-based scientists, from plant breeding, animal breeding, and microbiology sectors alike (WFSR report 2021.506, page 27, page 44, page 51).

The European network for GMO laboratories (ENGL) states that the required specificity for genome edited plants in detection methods will most likely not suffice in case the genome edit is a non-unique DNA alteration that is indistinguishable from naturally existing variants. In addition, detection of the presence of unauthorised genome-edited plants is not possible, and market controls will fail, as the origin of a DNA alteration cannot be established (ENGL, 2019).

Although the ENGL report was specific for plants, the outcome would also apply for animals and microorganisms containing small genetic alterations.

Member states are currently not enforcing GMO legislation for genome-edited products with small genetic alterations for various reasons. One of the most prominent reasons is the lack of reliable detection methods and the considerable cost to develop these methods combined with a limited trust in success. In addition, some member states gave legal reasons not to enforce, such as that the member state has a general definition for NGTs at national level, or that no amendments to GMO enforcement provisions had been made so far, (EC report, page 26). Finally, the lack of evidence of NGT products on the market was also given as a reason not to enforce, although this is likely to change given the developments on non-EU markets.

Definitions of certain concepts are still missing (e.g., mutagenesis)
Despite the clarity given on how mutagenesis techniques should be regulated and the status of the exempted techniques in the court ruling of the CJEU in Case C-528/16, there are still concepts that are not clearly defined. "Mutagenesis" for example, is not defined and the CJEU referred to other texts in the legislation to explain the concept.

The Commission staff working document gives a list of other terms whereby the legal interpretation are not clearly established, namely "conventionally used in a number of applications", "long safety record", "altered" (in altered genetic material), "alteration of genetic material", "recombinant nucleic acid molecules", "use of recombinant nucleic acid molecules" and "transformation event" (page 54-55 of (European Commision, 2021b)) Thereby, several uncertainties remain in the existing regulations for a clear definition of genetic techniques that are included/excluded.

GMO definition not in line with those elsewhere
The most widely recognized definition for genetically modified organisms is from the Cartagena protocol on biosafety. The protocol defines a living modified organism (LMO) as "any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology" (*Cartagena Protocol on Biosafety*, 2000). Thereby, modern biotechnology is defined as "a) in vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or b) Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection;". Small genetic modifications, such as indels introduced by genomic techniques, may not contain a novel combination of genetic material, or at least not a novel (trans)gene.

A widely recognized definition enables trade and prevents international disputes and problems. This was elaborated upon in the interview on the case of Argentina (Interview Argentina, Annex 1.1), which has adopted the Cartagena Protocol definition on Genetic modification, despite not being one of the parties to the Cartagena Protocol.

Not science-based
The interviewed experts clearly indicated a lack of science-based and risk-based reasoning in the current GMO legislation (WFSR report 2021.506, page 29), while science-based reasoning is desired (WFSR report 2021.506, page 29,31 and 55). It is considered incompatible that additional safety assessments are needed for products developed with directed mutagenesis techniques (NGTs), while such assessments are not needed for products developed with conventional mutagenesis techniques with randomly introduced mutations, which are considered safe based on their history of safe use (WFSR report 2021.506, page 48, and 52).
It has to be noted that these comments pertain to the plant and microbiology sectors, where selection procedures for the organisms with the correct modifications are common. These selection procedures are not only needed for agronomic reasons, but also because crossbreeding may introduce undesired edits or mutations as well (WFSR report 2021.506, page 52). This can be the case when a conventional variety is crossed with a wild variety, for example.
Overall, experts consider that the safety assessments required for genome-edited organisms under the existing GMO legislation are not proportionate to the food safety and environmental risks they pose. Nevertheless, it may be argued that the discussion on the regulation of NGTs goes beyond safety, and also touches upon the wider societal impacts and normative values (Mampuys, 2021).
In the experience of the FSANZ, the process-based definition leads to much scrutiny in the product assessment, which is not in proportion to the food safety risks they pose (Interview Australia, Annex 1.2)

Discrepancy between mutations generated by de-regulated random mutagenesis versus strict regulations for precise genome editing techniques
Connected to the previous comments on the legislation not being science-based, is the discrepancy in the way mutations from NGTs and random mutagenesis are judged. Both techniques can be used to introduce mutations in the genome of organisms; but while NGTs work in a more targeted manner, with a limited amount of mutations overall, random mutagenesis creates many mutations in various locations in the genome (Sturme, van der Berg, et al., 2022).

In essence, the mutations that are introduced by both techniques are similar when considered at the DNA level: being the introduction, deletion or substitution of one or a few base pairs. A desired mutation may be obtained by either technique. However, these mutations are judged in a different way from the legal perspective, due to the history of safe use for the random mutagenesis techniques, while such a history of safe use does not exist for NGTs. Thus, the discrepancy is that similar mutations are treated differently due to the process of the introduction of the mutation, although the nature of the mutations on a DNA level is similar.
This discrepancy between mutations induced by random mutagenesis versus mutations induced by NGTs is relevant for the plant breeding sector and industrial microbiology (WFSR report 2021.506, page 52, 53) but not for the animal sector, where random mutagenesis is not commonly used.

Not fit for future genetic engineering developments
The GMO legislation was drafted two decades ago, based on the developments in genetic engineering at the time. Since then, the developments in biotechnology have been considerable, with genome editing techniques as one of the most prominent innovations. The legislation was not drafted in a way prepared for such developments. Indeed, the EC reported that GMO legislation is "not fit for purpose for some NGTs and their products".
Novel technologies that are now only at the horizon (such as epigenome editing) or future technologies that are not yet developed could pose challenges in the future.

Precautionary approach: no steps taken to take away uncertainties
The precautionary principle enables regulatory, preventive action in case of unknown risks for the environment, or for human, animal or plant health (Mampuys, 2021).
The precautionary principle is explained in the document 'Communication on the Precautionary. Principle' (European Commision, 2000). This principle is only relevant in case of a potential risk and has 6 conditions for precautionary measures. One condition includes the facilitation of scientific data for a more comprehensive risk assessment. This additional data collection is generally lacking or at least is not actively pursued for current GMOs.
The view of Food Standards Australia New Zealand (FSANZ) is that the current approach may have been justified 25 years ago, because of uncertainty with new technologies, but that this is no longer the case (Interview Australia, Annex 1.2).

3.2.3 Opportunities / Positive implications

Potential for clear positioning of organic and/or GMO-free products
Currently, products sold as organic in the EU should not be or contain GMOs, according to Regulation (EU) No. 2018/848. Under the current regulatory situation, also gene-edited products cannot be labelled and sold as organic. Yet gene-edited crops could still pose problems in case there is a lack of sufficient organic supplies. In that case, they may be adventitiously present in conventional materials sourced by organic farmers, such as is allowed under EU legislation on organic farming [Annexes V, VI, VIII, IX, and XI of Regulation (EC) No 889/2008). NGT products may threaten the feasibility of compliance and segregation of organic farming and conventional farming (European Commision, 2021b). Under scenario A, the cultivation and admixture of NGT crops will likely be very limited, because of the high costs associated with approval. Therefore, the European organic sector will likely not have to deal with problems of segregation of products and avoids the increase of costs to ensure the absence of NGTs in their products.
Certain forms of genome editing (particular SDN1, and some cases of SDN2 or SDN3) do not fall under GM techniques in other jurisdictions (such as Japan, Argentina, Brazil) and are not regulated there, the organic sector in these countries will likely find it increasingly challenging to avoid genome edited products altogether. In addition, more European farmers may be tempted to start with organic production under current regulations, when their advantage in conventional agriculture is reduced compared to farmers worldwide (Purnhagen 2021).
Consumers from outside the European Union may come to prefer European organic products, due to the guarantee that these products will remain unmodified by modern genetic techniques. This would be particularly relevant for food crops.
Nevertheless, it is not given that the organic sector will strengthen in this scenario, as it depends on how the organic sector outside the European Union treats the NGTs. In the case that NGT derived plants are allowed in the organic sector outside the EU, the comparative advantage vanishes (Purnhagen 2021).

3.2.4 Threats / Negative implications

Negative impact on innovation
The current European legislation allows cultivation of GM plants or breeding of GM animals in the EU only under very strict conditions, and the legislation is not considered stimulating for the development of NGTs in the academic and industry sectors. The lack of opportunities to do research and get experienced with techniques, was expressed particularly in the animal sector (WFSR report 2021.506, page 38). Some plant breeding programs may be moved to non-EU countries (WFSR report 2021.506, page 30).
Current process-based regulations in Australia are considered to not promote innovation, and this is considered to be true worldwide (Interview Australia, Annex 1.2).

Impact on competitiveness EU business
This threat is linked to the previous one, the impact of innovation. When there is a lack of opportunity or a limited opportunity to work with, perform research on, and gain experience with new techniques, economic opportunities may be lost. This could be a long-term process, as for example genomics in the animal sector took 25 years to develop, while now benefits are seen (WFSR report 2021.506, page 38).
The impact on the competitiveness of the European Union is particularly a threat for the plant breeding and microbiology sectors. One of the most important arguments heard from experts is the shorter development times for new varieties with NGTs compared to current methods (WFSR report 2021.506, page 29). Non-EU businesses will likely have an advantage over EU-based companies with these shorter development times. Furthermore, the costs of bringing a crop obtained with NGT to the market are higher (Purnhagen & Wesseler, 2021). The competitiveness of European farmers may be at stake as well, when they are not able to cultivate crops obtained with NGTs, whereby their comparative advantage may be reduced (Purnhagen & Wesseler, 2021).
The loss of competitiveness of European companies from the industrial microbiology sector compared to those from outside Europe is feared, not only because of a lack of use, but also because of long approval procedures (WFSR report 2021.506, WFSR report 2021.506 workshops, page 53, page 55).
In the animal breeding sector, the expectations of possibilities for gene editing are somewhat limited as compared to the plant and microbiology sector in light of current breeding practices. Multiple breeding lines will have to be edited, and fundamental knowledge on genes and their effects will be a bottleneck (WFSR report 2021.506, page 38). The rules for animals are more stringent in some countries that have less stringent rules for plants obtained with NGTs, such as the United States.

Another concern that is shared in the plant, animal and microbiology sectors is that mainly larger companies benefit from strict regulation, as they have the financial resources that are needed to comply with the regulatory needs. Small and medium-sized enterprises (SMEs) have less opportunities to utilize new technologies. This is a concern, in particular compared to other jurisdictions, such as the USA, Argentina, and Japan (WFSR report 2021.506, page 29 page 38, page 55). This is recognized by FSANZ for "conventional GMO's", for which it has not seen applications from small or medium-sized companies under their process-based approach (Interview Australia, Annex 1.2).

Nevertheless, not all stakeholders are convinced that the benefits are considered hypothetical and achievable by means other than biotechnology (European Commision, 2021b).

Accidental use of NGTs
In other countries in the world, there are different rules on when NGT derived organisms count as GMOs. There are multiple examples where certain organisms with small edits are excluded from regulation, such as USA, Japan, Argentina, Australia, etc, although the exact conditions may differ per country. When a NGT product is excluded from regulation, it may not be distinguishable from conventional products for operators in the agri-food commodity export chains in these countries.
This could bring about difficulties for EU importers of products and seeds, as they may not be aware of the exact procedure used to obtain a crop, product, or seed. There is a risk that European operators will accidentally, without the intention to do so, use NGT products
Given the difficulties with detection and identification, there will also be limited opportunity to verify the NGT-free nature of an import product.

Barriers to international trade
Before GMOs that are approved in other parts of the world may be imported into the EU, they have to be approved in line with the GMO legislation. This holds true for GMOs obtained from NGTs as well, although these may be exempt from regulation in the country of origin (see above). Therefore, no safety assessment may be available, and moreover there may not be a reliable detection method available for the NGT-derived GMO.
As a result and in order to prevent the presence of unapproved GMOs in import, the EU may want to ban all imports from a certain crop from other countries altogether, when there are NGT-derived commodities of that particular crop cultivated there (Purnhagen & Wesseler, 2021).

Revert to CJEU each time the applicability of the legislation to a new breeding innovation needs to be clarified
Developments in biotechnology will continue. The most notable change with the introduction of directed mutagenesis techniques led the highest administrative court in France to seek clarification on the status of products from these techniques as GMOs (and whether they are also eligible for exemption) from the CJEU under case C-528/16. There is a risk of recurrence for other novel breeding technologies being developed for which the legislation is also unclear, in which case the CJEU would have to be asked for clarification once again (European Commision, 2021b). This could be for novel technologies that are on the horizon (such as epigenome editing) or technologies that are still experimental.

Labelling duty not enforceable
Under the current legislative framework, GMO foods, hence also genome-edited products, have to be labelled according to Regulation (EC) No. 1829/2003 and Regulation (EC) No. 1830/2003. The duty to inform consumers is adhered to, this is important because the freedom of choice for consumers is highly valued in the EU. However, it will be hard to enforce the current regulations for labelling of GM products for certain genome-edited products due to the problems with the detection and the identification of small edits. Therefore, the authorities will not be able to ensure that correct information is given to the consumers. What makes the situation even more complicated, is that GMO labels may scare consumers, and lead to stigmatization of genome editing techniques. In addition, labelling systems can be costly by themselves (Scott et al 2018; WFSR report 2021.506, page 53; page 55). There is a chance certain producers might be tempted not to label their product.
Even modifications that could enhance the safety of a product, such as deletion of an antibiotic resistance gene or a toxin related gene, would have to be labelled.

Potentially easy to circumvent legislation
In line with the difficulties for establishing detection methods and the inability to enforce the legislation, there is a risk that the less law-abiding developers will try to circumvent the legislation, and not subject genome edited organisms to the required risk assessment. Thereby, the developers adhering to the regulations will be disadvantaged, as they will spend considerable efforts on the practices required.

3.3 Other considerations for Scenario A

Experts from the plant and microbiology sectors believe that there are cases whereby NGTs can actually enhance the safety of products. Experts from the plant breeding sector estimate that the occurrence of unwanted effects may be lower with NGTs, compared to conventional breeding techniques (WFSR report 2021.506, page 22; WFSR report 2021.506 workshops page 52). The experts considered in particular for cross breeding the chance of unexpected changes in the final product, due to unknown effects at the DNA level (WFSR report 2021.506, page 52). Experts from the microbiology field agree that safety risks can be reduced with NGTs, compared to conventional techniques such as random mutagenesis (WFSR report 2021.506, page 44-45; page 55). Particularly in combination with the controls and screening based on sequencing of the entire genome of the microorganisms. None of the interviewed experts expects unsafe products due to new techniques in microorganisms (WFSR report 2021.506, page 42).

4 Scenario B: Risk assessment adjusted

4.1 Description of scenario B

In scenario B, the current GMO legislation is retained, although the guidance for risk assessment is altered. Owing to higher precision, SDN-1, 2, and 3 edited organisms would require less safety data than GMOs developed by conventional transgenesis.
The opinions of the European Food Safety Agency (EFSA) on plants developed with SDN-3 (EFSA GMO Panel, 2012) and on plants developed using SDN1, SDN2 and ODM (EFSA GMO Panel, 2020) are used as a reference. These opinions concluded that the guidance for GMOs is only partially applicable for plants obtained with SDN and ODM. Not all data required for GMOs is needed and available, it depends on the exact application what data is needed.
Data required for risk assessment will entail those on the modified trait, while evaluation of the genomic context would only be needed for SDN-3 applications where recombinant DNA is introduced via homology directed repair, but not for SDN-1 and SDN-2 applications. Data requirements may be limited, for example, to molecular characterization, bioinformatics and phenotype analysis.
Of note, the data required for risk assessment in this scenario should still be sufficient to reach the conclusion that the new GMO is as safe as a conventional counterpart already on the market.

As this scenario is similar to scenario A from chapter 3, the current EU legislation, there is overlap in the analysis table.

Table 4 *Analysis of scenario B: the current EU regulation with an adjustment of the risk assessment for GMOs, particularly those obtained by new genomic techniques.*

Scenario B: Current EU regulation with adjusted risk assessment	
Strengths / Advantages	**Opportunities / Positive implications**
• No need for fundamental adaptations of current regulation • Risk-based analysis possible • Safety of genome editing techniques can be verified • Clear GMO definition* • Alignment with precautionary principle*	• Shorter safety dossiers may decrease approval time and financial burden of dossiers • Enables use of gene editing techniques to some extent
Weaknesses / Disadvantages	**Threats / Negative implications**
• Difficult to establish detection strategies for small genome edits* • Definitions of certain concepts are still missing (e.g. mutagenesis)* • GMO definition not in line with those elsewhere (e.g., different from LMO in Convention on Biological Diversity, Cartagena Protocol)*	• Impact on innovation* • Impact on competitiveness EU plant sector* • Revert to CJEU each time the applicability of the legislation to a new breeding innovation needs to be clarified* • Labelling duty not enforceable*

The * ind cates this argument is the same as for scenar o A.

4.2 Analysis for scenario B

4.2.1 Strengths / Advantages

No need for fundamental adaptations of current regulations
With changes in the risk assessment, the core of the legal framework for GMOs does not have to be changed. However, there is a need for amendment of the Implementing Regulation (EU) No. 2013/513, Annex I and Annex II,with the exact description of the information that has to be provided for safety assessment.

Risk-based analysis possible
A scientific approach that is in proportion to the risk is possible. Experts widely agree that this is the most suitable approach for the judgement of new products.

Safety of genome editing techniques can be verified
One of the main strengths of this scenario would be the information that is generated for the applications of genome editing techniques. In this scenario, risk assessments would still have to be done by the developers of genome-edited products before their product are allowed to be brought to the market. The information from these assessments would provide information on the actual food safety of genome-edited crops and food products. In this scenario, this information is targeted towards the particular genome techniques that are in use. This could entail for example information on off-target modifications and the consequences for safety, and to what extend unintended effects of on-target modifications do occur. Requesting specifics for the experimental conditions (type of editing tools, concentrations, number of replications, number of cells with (un)successful transformations) can further optimize processes.
The information collected may in turn lead to better instructions, more concise risk assessments, or a very strong argument for redefining legislation.

Clear GMO definition
This is as in scenario A, thus see chapter 3.2.1.

Alignment with precautionary principle
This is as in scenario A, thus see chapter 3.2.1.

4.2.2 Weaknesses / Disadvantages

Difficult to establish detection strategies for small genome edits
This is the same as with the current situation, see chapter 3.2.2. It is difficult to establish detection strategies for small genome edits, such as base editing (nucleotide substitutions) and small insertions or deletions, and it is momentarily seen as impossible to establish with certainty the origin of an edit.

Potentially easy to circumvent legislation, as gene edits cannot be easily recognized
This is as in scenario A, thus see chapter 3.2.2.

Definitions of certain concepts are still missing (e.g. mutagenesis)
This is as in scenario A, thus see chapter 3.2.2.

GMO definition not in line with those elsewhere
The current GMO definition of the EU would remain in place, thereby differing from the definitions utilized in certain other parts of the world, and the Cartagena protocol (See chapter 3.2.2) for more details.

4.2.3 Opportunities / Positive implications

Shorter safety dossiers may decrease approval time and financial burden of dossiers
The current safety dossiers are seen as a financial burden by industry (WFSR report 2021.506, workshops, page 55). In this approach, the burden may be lower, at least for certain products, which may lead to more applications. Therefore, more knowledge may be obtained on the potential hazards and the safety of NGTs. In time, guidelines for safety dossiers may be further specified or narrowed, with the new knowledge. There may be more opportunities for small and medium-sized companies to file a dossier, something that seems now particularly feasible for larger companies (WFSR report 2021.506, page 29 page 38, page 55).

Enables use of gene editing techniques to some extent
Compared to scenario A, this scenario enables the utilization of gene editing techniques. The acclaimed contributions of NGTs to sustainability goals may be realized within this scenario. It might serve as an temporary solution, in the procedure to a more substantial change in legislation. Furthermore, with the development of technology and further insights in the use of NGTs, it will become clearer if further alleviation of guidelines may be possible.

4.2.4 Threats / Negative implications

Impact on innovation
This is comparable to scenario A, but may be less pronounced.

Impact on competitiveness EU plant sector
This is as in scenario A, thus see chapter 3.2.4.

Revert to CJEU each time the applicability of the legislation to a new breeding innovation needs to be clarified
This is as in scenario A, thus see chapter 3.2.4.

Labelling duty not enforceable
This is as in scenario A, thus see chapter 3.2.4.

4.3 Other considerations for scenario B

During the high-level event on 29 November 2021 on "New genomic techniques - the way forward for safe and sustainable innovation in the agri-food sector" (European Commission, 2021), an option similar to this scenario was discussed. In addition, the option to add an assessment of sustainability besides the safety, was also discussed.

This scenario enables knowledge development into the potential (absence of) safety consequences, based on the safety assessments that are performed on NGT products. It may be worthwhile, from a safety perspective, to re-evaluate the safety standards based on the insights gained over time. Nevertheless, other considerations, for example on sustainability, societal impact or general consideration can be valid as well.

Another avenue for altering technical information requirements for the environmental risk assessment of GMOs with which substantive experience has been gained is through a so-called differentiated procedure. The opportunity for member states to hand in a proposal for a differentiated (simplified) procedure is offered in Article 7 of Directive 2001/18/EC. The European Commission is then to consult other member states' competent authorities as well as relevant scientific committees. The decision should state the minimum amount of data (from Annex III of the same Directive) that has to be required under the proposed procedure. The reason why this option has never been used is presumably because it would still require consensus amongst member states, which might be difficult to achieve (Kearns et al., 2021).

5 Scenario C: Small edit exemption

5.1 Description of scenario C

In scenario C, the current EU GMO regulation remains in place, yet certain small gene edits induced by NGTs will be exempt from GMO legislation. The definition of GMO remains process-based. Exempted are SDN-1 edits, resulting from DNA repair following non-homologous end-joining, and SDN-2 edits resulting from DNA repair with a template for the desired genetic alteration. The exemption is only applicable to GMOs with a single edit. They are treated the same way as random mutagenesis techniques (by means of ionizing radiation or use of mutagenic chemicals). Products with SDN-3 edits will require full approval.

This scenario may be brought about by changes in the exemptions listed in the Annex of Directive 2001/18/EC. Another alternative is redrafting legislation, whereby the definition of what is considered genetic modification is revised, so that certain smaller edits are not considered GMO anymore.

Scenario C has similarities to the regulatory situations in Japan and Argentina. Japan has adopted regulations that exempt certain small genomic changes and edits from the GMO legislation. Organisms with SDN-1 edits are not considered to be GM organisms, which aligns with the definition for a LMO under the Cartagena Protocol definition (Interview Japan - OECD, Annex 1.3, (Tsuda et al., 2019)). For genome edited foods, not only SDN-1 derived but also certain SDN-2 derived foods are exempted. These are SDN-2 foods whereby no transgenic element remains and whereby the change at the DNA level is the insertion, deletion or substitution of several bases.
In Japan there is also a consultation procedure in place, whereby applicants exchange information with the relevant ministry to see if the organism or product needs a safety check. The relevant ministry can be the Ministry of Health, Labour and Welfare for foods derived from genome editing techniques for example, and the Ministry of Agriculture, Forestry and Fisheries for genome-editing derived feeds. If no safety assessment is required, a public notification can be issued specifying the organism and the changes made to it. Strictly speaking the consultation and with it the notification are not mandatory, but strongly recommended (Interview Japan - OECD, Annex 1.3).
In Argentina, GMO legislation applies for organisms with a novel combination of DNA. More specifically, the definition used is similar to the definition of LMO in the Cartagena protocol, except that the word “living” was excluded. An organism is considered a GMO when there was use of a modern biotechnology, and when a novel DNA sequence was created (Interview Argentina, Annex 1.1). The National Biosafety committee CONABIA (the Argentine National Advisory Committee on Agricultural Biotechnology), with representatives from various ministries and universities, judges whether an organism is considered a GMO.
Within the EU, with national competent authorities acting as the obvious first point of contact for product developers, this could follow a notification procedure similar to what has been implemented for other products, such as traditional foods under the novel foods legislation. Under such a regime, a member state authority would find that a new product (intended for commercialization or large-scale field release) does qualify for exemption and will notify this to the European Commission. During a commenting period, other member state authorities and the Commission will be able to comment on the proposed exemption. In case of sustained safety objections against exemption, the case may be relegated to EU risk assessment bodies for a full assessment (as an application instead of a notification).

Table 5 *Analysis of scenario C: some types of small edits will be excluded from GMO regulation, but the definition of GMOs remains process-based.*

Scenario C: Small edit exemption	
Strengths / Advantages	**Opportunities / Positive implications**
• Feasibility for enforcement: no need to distinguish small edits from natural genetic variation; detection possible of foreign vs endogenous DNA • Fast implementation of exemption into regulation possible • Labelling obligation enforceable	• Knowledge development in Europe by enabling use of gene editing techniques • Competitive situation of Europe
Weaknesses / Disadvantages	**Threats / Negative implications**
• Organisms with multiple (complex) mutations are still difficult to judge • Definition of a small edit is arbitrary • "perfect allele replacement" not exempted and still subject to GMO legislation • Small mutations may have great consequences on safety and animal welfare	• Regulation may not be future-proof • Potential negative public opinion due to addition of exemptions • Organic sector viability may be disadvantaged • Other changes in the food system may receive less attention • Regulations (bans) on national level

5.2 Analysis for scenario C

5.2.1 Strengths / Advantages

Feasibility for enforcement: no need to distinguish small edits from natural genetic variation; detection possible of foreign vs endogenous DNA

One of the main strengths of this scenario is that the products that would be exempted, would be those with only endogenous DNA. Small edits that are not distinguishable from naturally occurring modifications or modifications induced by exempted, conventional mutagenesis techniques would fall outside the regulation and no detection methods would be needed. Organisms with foreign, transgenic, DNA would still be regulated, and currently existing DNA-based detection can be used for their detection.
Novel combinations of DNA that still have to be labelled as GMO can be detected, and therefore there is no negative influence on enforceability.

One of the main strengths of the Japanese regulation is the enforceability of the requirement for GMOs to be traceable. Transgenic products will be detectable, while conventional mutagenesis products do not require detection/traceability (Interview Japan - OECD, Annex 1.3).

Fast implementation of new regulations and feasible solution

This scenario could be implemented rapidly, but would only be a strength if it is accomplished via an amendment of the annex with exemptions of Directive 2001/18/EC. The fast implementation is particularly seen as a strength by stakeholders from the breeding sectors (WFSR report 2021.506, page 51, 53). The drafting of new legislation would take a longer time.

Labelling obligation enforceable

As with this scenario the enforcement of the GMO legislation is feasible (see above), also the labelling obligation dictated by the European law is enforceable in this scenario. Small edits would be exempt from the GMO legislation, and therefore products with a single small edit will not have to be labelled.
However, the labelling of transgenic products would remain mandatory, as it is in the current situation.
A similar situation is in place in Japan, where products with small edits are exempt from a labelling requirement, but the labelling of transgenic products is still mandatory (Interview Japan - OECD, Annex 1.3). (The ability to enforce the legislation is important in Japan, also when it comes to labelling. Therefore, labelling is only obligatory when the product contains a newly expressed protein and/or recombinant DNA (Interview Japan - OECD, Annex 1.3) This is different from Europe, where also products such as oils (without newly expressed proteins or recombinant DNA) have to be labelled when derived from transgenic plants.

Given the importance that the EU places on informing the consumer of product attributes, it is a strength that the authorities will be able to verify compliance with the labelling requirements.

5.2.2 Weaknesses / Disadvantages

Organisms with multiple (complex) mutations are still difficult to judge
In case of the introduction of multiple small edits (SDN-1 and SDN-2) in parallel, this could still be problematic as it remains unclear how these would be considered under a scenario with small edit exemptions (WFSR report 2021.506workshop page 53).
So far, there is limited experience with multiple small gene edits induced by NGTs. Some studies published results on multiple gene edits into yeast (e.g., (Utomo et al., 2021; Yang et al., 2021) and plants (e.g., (Yang et al., 2021)), yet this is in the (early) research stage. However, there are many agronomically interesting traits that are controlled by multiple genes, such as drought tolerance, that are relevant.

Japan and Argentina, where SDN-1, and to some extent SDN-2, organisms fall outside the scope, have systems in place which would at least alert the authorities if organisms with multiple mutations are made. Japan does have a system of mandatory notification of genome edited organisms, whereby in the procedure it can be decided by the relevant ministry if an additional safety check is needed (Interview Japan - OECD, Annex 1.3). In Argentina, there is a system in place for controlling new varieties, also from other breeding methods. Hereby a risk assessment process can still be started (Interview Argentina, Annex 1.1).

Definition of a small edit is arbitrary
What qualifies as a "small" edit would have to be clarified further, to avoid uncertainty and unclarity.
The possible unclarity is exemplified by the Japanese situation, where the criterion "several bases" is given, which is not concrete and undisputable. The consequence may be that Japanese developers will prefer SDN-1 over SDN-2 applications, to avoid the uncertainty, although so far there it is too early to say if this will be the case in practice (Interview Japan - OECD, Annex 1.3).
Clarity could be achieved by making distinctions between SDN-1, SDN-2, and SDN-3, possibly including a cap on the number of nucleotides that are mutated by the edit. There could be examples of edits that pose difficulties for such a categorization, though, such as a perfect allele replacement with SDN-3.

"Perfect allele replacement" not exempted still subject to GMO legislation
While edits with SDN-1 and SDN-2 are exempt from regulation, edits obtained with SDN-3 are not. SDN-3 can be used to exchange alleles between varieties of the same species, the so called "perfect allele replacement". In such a case, the detection mentioned under 5.2.1, based on foreign DNA, would not be possible.
This example was brought forward in the Argentinian interview, where, due to the definition based on the Cartagena protocol, this could be exempted as it is not a novel combination of DNA (Interview Argentina, Annex 1.1). There has been a case where a whole allele was transferred from one variety to another, with varieties from the same species and the same location in the DNA (Interview Argentina, Annex 1.1)

Small mutations may have great consequences on safety and animal welfare
The size of an edit is not predictive for the impact of the mutation. While this concern is particular in the animal sector, where it is recognized that any mutation may negatively affect animal health and welfare (WFSR report 2021.506, page 36). Long term studies may be needed to assess the true effects of small edicts on animals. Therefore, this regulation may be suitable to regulate genome edited animals.
Nevertheless, the fact that small mutations can have large consequence also holds true for plants and micro-organisms (but this might only indirectly affect the health of human and animal consumers in theory). In addition, this concept is not limited to induced mutations, since also spontaneous mutations may have great consequences.
The exemption of SDN-1 and SDN-2 edits does not mean that products obtained with genome editing that would have a small mutation with a safety consequence, would automatically be marketed. For conventional crop development, compounds with known negative effects are a point of attention (WFSR report 2021.506, page 28). OECD has published consensus documents on the main agronomic crops, that gives an overview of i.a. common nutritional composition and the relevant allergens, toxins, and anti-nutritional factors per crop

(OECD, 2021). In microbiology, it is common practice to consider the safety when developing a new strain (WFSR report 2021.506, page 46).
The General Food Law ensures no unsafe food may be marketed (Regulation EC 178/2002).

5.2.3 Opportunities / Positive implications

Knowledge development in Europe by enabling use of gene editing techniques
When certain types of edits (i.e., SDN-1 and SDN-2) obtained via gene editing are excluded, it would be easier to employ gene editing for both academic and corporate research. Obtaining research funds would become easier for academic researchers and the consortia that they build with corporate partners when the investigated plant or product is not considered GMO. In addition, conducting field trials with NGT crops will be less cumbersome when there is no need to adhere to the GMO legislation. Further knowledge could be developed, and experience gained in Europe, not only in other parts of the world. The relocation of plant breeding programs to non-EU countries (WFSR report 2021.506, page 30) may be prevented.
In Japan, the authorities wanted to stimulate development of gene-edited organisms with the new regulations introduced in 2019. A clear relationship between this policy and innovation is starting to emerge, as a number of gene edited products have been developed since then (Interview Japan - OECD, Annex 1.3)

Competitive situation of Europe
As for knowledge development, this scenario also creates economic opportunities. EU-based companies could benefit from advantages such as shorter development times for new varieties (WFSR report 2021.506, page 29). In addition, if no (elaborate) safety dossiers are needed for genome edited organisms with a small edit, this will decrease the costs to bring a new product to the market significantly. Also SMEs will be able to utilize the technologies more (WFSR report 2021.506, page 29 page 38, page 55). In Argentina, the majority of NGT products presented to the regulatory authority have been developed by local companies, public research institutions, and foreign SMEs (91%). For "conventional" GMOs, SMEs only represented 10%, while the other products were presented by foreign multinationals (Whelan et al., 2020).
The potential opportunities for the competitive situation are mainly in the plant breeding and industrial microbiology sector. The extent to which this is positive for the competitive situation, will depend on how promising gene editing will prove to be.

5.2.4 Threats / Negative implications

Regulation may not be future-proof: new types of edits may be developed
With continuous developments, it is unclear to what extent other techniques or modifications might be invented and used in the future. Evaluations on how these would fit into the regulations, with further exemptions and specifications are likely to occur. This may endanger the competitive situation of the EU in the future.

Potential negative public opinion due to addition of exemptions
While scenario A can be seen as most in line with the public opinion, there is a threat that in this Scenario C, the public may not respond well. In general, the public does not consider more conventional GMO techniques and gene editing techniques to be very different and prefers the conventional breeding methods. It could be seen as "tampering with" definitions (WFSR report 2021.506, page 53).

Organic sector viability may be disadvantaged
The co-existence of organic farming and regular agricultural production may be troublesome (EC report, page 40). The traceability and labelling requirements may be difficult to ensure for the organic sector. To keep production of organic separated from NGT products, may lead to increased costs, and presence of NGT products may be hard to avoid. This may all result in a loss of consumer trust. There may be options for document-based traceability, although these are considered costly (European Commision, 2021b).

Other changes in the food system may receive less attention
During the EC high-level event in November 2021 (European Commission, 2021), one concern was that allowing NGTs may result in a focus on technical revisions in the food system. To be able to reach the goals of the Green Deal and implement the Farm-to-fork strategy, many changes to the food system will be

necessary. There is the threat that too much focus goes into creating new crops and organisms with NGTs, whereby other changes (e.g. changes in framing practices, land use, dietary patterns) may receive less attention or may not be implemented at all.

Regulations (bans) on national level

Within the GMO regulations in the European Union, member states have the opportunity to regulate products at a national level as well. In the decision of the CJEU in Case C-528/16, the CJEU stated that the products resulting from exempted techniques may still be regulated at a national level if they pose the same risks as non-exempted GMOs (such as in the example of herbicide-tolerant crops). Therefore, there is the risk that some member states will ban certain exempted NGT products from their own markets, which in turn threatens to result in fragmentation of the EU market (Eriksson et al., 2020). Yet any technical regulation that a Member State wishes to introduce must be submitted to the European Commission first. There should then still be a possibility for member states to comment on it, so as to ensure that it will not impede free movement and trade of goods and services within the European community under Directive (EU) 2015/1535 (2015/1535/EU).

5.3 Other considerations for scenario C

As mentioned in 5.1, this scenario has similarities to the situation in Japan and Argentina. However, in our scenario, no notification obligation or committee to assess the plant or product with a particular edit is included. An exemption in combination with a (obligatory) notification procedure may be an option as well, whereby the developer informs the regulator about products with small edits. This has as an advantage that regulators have insight in the development of new products with NGTs and can be published for the sake of transparency towards the public.

However, such a notification procedure changes two aspects of scenario C that were introduced as a strength. The enforcement of such an obligatory notification procedure may be very difficult, due to the problems that small edits are not distinguishable from naturally occurring edits. The implementation of the legislation will likely not be as fast anymore, as a new procedure would have to be implemented in the legislation, along with the designation of an authority or authorities to handle the notifications.

6 Scenario D: Product-based regulation

6.1 Description of scenario D

In this scenario, it is decided on a case-by-case basis whether a new product must be assessed for safety. The way the new product was created is not the determining factor. For example, for a new crop variety it does not matter whether it has been created by means of conventional breeding, mutagenesis breeding, "conventional" GM techniques, genome editing techniques or any other way: Only the novelty and risk characteristics determine what type of safety assessment is needed, whereby novelty is defined as something that has not been an attribute of this organism or product before. "Novel" would also include novel genome edits (be it SDN-1, 2 or 3) that have not been seen before. Product developers will be able to consult with authorities whether their product is novel or not. In a product-based scenario, the precautionary principle for new techniques is abandoned, as it is only the safety of the end-product that is relevant.

A similar scenario in which only novel organisms and novel genetic alterations require regulatory approval is currently in place in Canada and the USA for novel organisms, foods and feeds.

Table 6 *Analysis of scenario D: a product-based regulation, whereby the necessity of a safety assessment is decided on a case-by-case, based on the characteristics of the end-product.*

Scenario D: Product-based legislation.	
Strengths / Advantages	**Opportunities / Positive implications**
• Pragmatic, case-by-case approach, with risk assessments tailored to the particular product • Future-proof regulation • Principle of equivalence: a product-based approach enables similar modifications to be assessed in a similar way	• Enables use of gene editing techniques for food production • Competitive position of European companies retained
Weaknesses / Disadvantages	**Threats / Negative implications**

• Unclear what will be deemed "novel"
• History of safe use:
  ○ Cut-off moment and interpretation
  ○ Safety record of GMOs is not considered
	• Currently exempted new varieties may require approval under this scenario
	• Lengthy and costly approval procedures
	• Organic sector viability may be endangered

6.2 Analysis for scenario D

6.2.1 Strengths / Advantages

Pragmatic, case-by-case approach

In this scenario, a case-by-case approach focusing on the product characteristics is followed for the pre-market safety assessment and regulatory decisions on new products.

This way, the risk assessment can be tailored to the risk characteristics of a particular product ensuring that the requirements remain realistic, proportional, and science-based, as suggested by experts (WFSR report 2021.506, Page 29, 45). Microbiologists point this out as a great advantage, particularly for existing products with known risk profiles and in-depth knowledge on the genomic sequence (WFSR report 2021.506, workshop page 52).

The approach also allows regulators to exercise flexibility, even empowering them to deal with products that may be a risk but do not require an assessment under current regulations (e.g., products obtained with random mutagenesis techniques).

In their regulatory system, this flexibility is seen as a great strength by USDA, (Interview USA - USDA, Annex 1.9). Indeed, also Canadian experts from Health Canada (HC) see this flexibility as a main strength due to the fact that decisions are based on product characteristics (Interview Canada - HC, Annex 1.6).
A case-by-case approach for deciding if and to which depth a safety assessment has to be performed is generally viewed as best practice.

Future proof regulation
Regulations that take the end-product as a basis for the assessment needed, have the advantage of being considered future-proof: no new legislation is needed when new technologies are developed.
For example, Health Canada has no list of approved techniques, and therefore no separate decisions have to be made by the legislators when a new technology is developed and used to make food products (Interview Canada – HC, Annex 1.6). The Canadian Food Inspection Agency (CFIA) also indicates that its program can accommodate products from new technologies under the same operating principles (Interview Canada – CFIA, Annex 1.8) and that guidance may be updated in the future (Interview Canada – CFIA, Annex 1.8).
Nevertheless, countries with a product-based legislation have developed, or are in the process of developing, new guidance for the industry (Interview USA - FDA, Annex 1.5; Interview Canada – HC, Annex 1.6; Interview Canada CFIA, Annex 1.8; Interview USA - USDA, Annex 1.9), in particular to include more up-to-date information on products obtained with new technologies.
Thus, while no new legislation may be needed within a product-based legislative framework, the need to adjust guidance for new technologies may still remain.

Principle of equivalence
Within this scenario, the process used to obtain a particular food product does not matter. It is the end-product that determines if a safety assessment is needed, and what aspects have to be addressed in the safety assessment. The principle of equivalence thus applies to products under this scenario.
In the interviews, the experts from the Food and Drug Authority (FDA) value the fact that food products with identical characteristics are treated the same as a main strength (Interview USA - FDA, Annex 1.5).
This is particularly relevant for organisms that have a long history of use, such as baker's yeast and lactic acid bacteria, as their genomes have been altered both intentionally and accidentally by man, (WFSR report 2021.506, page 45).

6.2.2 Weaknesses / Disadvantages

Unclear, what will be deemed "novel"
Products with "novel" characteristics have to be assessed, while those with characteristics that have been used safely in the past, do not. However, defining and deciding what should be considered novel can be very difficult. Experience from Health Canada shows that there is a lot of ambiguity in the definition of a new or altered characteristic (Interview Canada - HC, Annex 1.6). Variance in existing characteristics can pose a real challenge, in particular what is the threshold for regular variation and an altered characteristic. There can be ambiguity in what is regarded novel, particularly in the environment (Interview Canada - CFIA, Annex 1.8).
Guidance has to be developed to help developers to see if their products are considered to have "novel" characteristics, nevertheless.
In Canada, there are also some problems with the setting of a precedent for a certain characteristic. For example, if a particular characteristic such as herbicide tolerance has been assessed in the past, it has to be assessed again when another plant with that characteristic is put forward for evaluation. There is no clear moment when a characteristic is no longer considered novel (Interview Canada - HC, Annex 1.6.)

History of safe use: cut-off and interpretation
Products that have a safe history of use, do not have to be regulated. However, the interpretation of what is a history of safe use, and what data is required to prove that there is a history of safe use can be challenging (Interview Canada – HC, Annex 1.6).

6.2.3 Opportunities / Positive implications

Enables use of gene editing techniques
When a product-based legislation is in place, the use of genome editing techniques may be stimulated. This is because the approval procedures for certain products obtained with the techniques will be shorter or may not be needed at all, in particular for small edits and edits that are already present in other varieties.

Competitive position of European companies retained
Marketing costs of products from new techniques can be lower, particular for those with small edits.
One of the main foreseen advantages for breeding companies is the shorter development times for new varieties with NGTs compared to current methods (WFSR report 2021.506, page 29).

6.2.4 Threats / Negative implications

Now exempt new varieties may require approval
Organisms developed with conventional techniques may contain novel characteristics. While these are now not regulated or exempt from GMO regulation due to a history of safe use, they may be regulated under a product-based regulatory framework. For plant breeders and developers of industrial microbes for food purposes, this is seen as a threat (WFSR report 2021.506, workshop page 51.). They fear conventional methods to develop new varieties and strains will be restricted and more burdensome.

The criteria for novelty and / or the procedure to decide what is novel, will determine if this a real threat. These criteria should ensure safety, without requesting data on products that have a very low risk profile. Experts from Health Canada expect that 99.9% of the conventionally bred products from plant breeding will not be considered novel, thus will not require a pre-market assessment (Interview Canada -HC, Annex 1.6). Their criteria for novelty are as follows:
'Foods that are not considered novel are foods derived from plants with genetic modifications that 1) do not alter an endogenous protein in a way relevant to allergenicity or toxicity 2) do not increase levels of a known endogenous allergen, a known endogenous toxin, or a known endogenous anti-nutrient beyond the documented ranges observed for these analytes in the plant species 3) do not have an impact on key nutritional composition or metabolism, 4) do not intentionally change the use of the plants, and 5) do not result in the presence of foreign DNA in the final plant product.'

Lengthy and costly approval procedures
There is the threat that with product-based regulations, approval procedures for genome edited organisms that are considered to be novel, will still be very lengthy and costly for developers.
This threat is particularly perceived by stakeholders from the plant breeding sector (WFSR report 2021.506 page 51). This threat has to be seen particular when comparing with scenario C (small edit exemption); and for products that now may be exempt.
To illustrate that approval procedures may be lengthy in a product-based regulatory system: Health Canada takes about 410 days to complete an assessment for a novel food product, which does not include the time needed by developers to obtain the required safety data (Interview Canada – HC; Annex 1.6).
Nevertheless, this seems a shorter process compared to the time it takes to get regulatory approval for a transgenic GMO in the EU, which takes on average 4.8 years (Jin et al., 2019).

Organic sector viability may be endangered
This is similar as under scenario C, so see 5.2.4.

6.3 Other considerations

Under the current GMO legislation in Europe, the applicant is obligated to provide a detection method for a GMO before it can be brought to the market (Regulation (EC) No.1829/2003; Regulation (EC) No.1830/2003). This enables traceability of GMOs, and also a way of checking if correct labelling is applied. The situation in the USA and Canada is quite different, as there is no mandatory traceability or the need to provide a detection method for products that have undergone a safety assessment (Interview Canada - HC,

Annex 1.6; Interview USA – USDA, Annex1.9). The private sector offers solutions for detection (Interview USA - USDA, Annex 1.9).
Here it is the question whether a detection method needs to be given for products that have undergone a safety assessment. Regular food traceability laws in the EU would apply, that would enable the recall of food products if necessary. Requesting additional detection methods may therefore not be necessary.

Linked to this is the concept of labelling. In the EU, labelling of food and feed containing GMOs is obligatory according to Regulation (EC) No. 1829/2003 and Regulation (EC) No. 1830/2003. In Canada, this labelling is optional[1]. That said, the oil of the genome-edited, high-oleic soybean has to be labelled, to indicate the changed composition (Interview Canada - HC, Annex 1.6).
Without mandatory labelling of GMOs, the choice for consumers to avoid food products that have been genetically engineered in anyway, will be more difficult. The organic sector may provide an alternative, or the GM-free sector.

[1] Per the first of January 2022, labelling of food products has become obligatory in the USA: food products have to be labelled with a symbol stating the food is bioengineered or derived from bioengineered, or there have to be directions on the package that consumers can use to find the information via mobile phone. The recently adopted American rules are very generic, below the species level. (www.fda/gov.food/agricultural-biotechnology/how-gmos-are-regulated-food-and-plant-safety-united-states).

7 Discussion & Conclusion

Four different legislative scenarios have been discussed for the regulation of genome editing techniques used in food and feed production. These scenarios follow a product-based (scenario D) or process-based (scenario A, B & C) approach. As is evident from both the interviews and workshops, in practice this distinction comes in different shades of grey. Regulatory approaches for these novel techniques vary greatly amongst the countries that were investigated. For example, in Canada, where a product-based legislation is in place which considers whether there is a novel property, transgenic organisms are always regarded as novel. In the United States, the situation is complex as the USDA APHIS (responsible for assessing plant pest, disease, and wheat risk) and the FDA (responsible for food safety evaluation) have different approaches regarding genetic techniques. The USDA considers gene editing as a form of genetic engineering, although organisms may be exempted when only minor DNA changes have been introduced. The FDA considers organisms (plant, micro-organism or animal) for assessment? only when there is a new additive present (NB "additive" has a different connotation under US law, requiring a pre-market safety assessment and authorization)[2], whilst the FDA does not necessarily consider small edits safe as they still may have a significant impact on product characteristics.
The responsibility for ensuring the safety of any food product (beyond additives) remains with companies. For example, the FDA will complete the consultation procedures for biotechnology products with a letter to the applicant in which they state that they have no further questions.

In the EU, the processes that are used to obtain a novel organism determine whether it is considered a GMO and will require a pre-market safety assessment. The safety assessment in itself is done on a case-by-case basis, whereby depending on characteristics of the organism and the introduced protein and genetic material, additional assessments may be needed.
Nonetheless it is important to emphasize that despite their divergent approaches towards gene editing, *transgenic* organisms do require a safety assessment in all countries studied.

Consultation procedure
Worldwide, various countries have introduced a consultation procedure for developers of new products obtained with NGTs that determines what safety assessment is required and if a product is considered a GMO.
In Argentina, a biosafety committee with members from relevant ministries and from universities, judges whether a genome-edited organism is considered a GMO, based on the presence of a novel combination of DNA and the use of modern biotechnology. There is the possibility to have a preliminary consultation at an early stage of development, enabling product developers to have a preliminary outcome, which can give direction to the developer and is useful in for example obtaining funding. Nevertheless, a definite decision is made when data are available.
In Japan, a consultation procedure with the relevant ministry (or ministries) can be done to decide if an organism obtained with a NGT requires a safety assessment. The consultation procedure is strongly recommended, but not mandatory (Interview Japan OECD, Annex 1.3).
In Canada, product developers are encouraged to consult with Health Canada (HC) and the Canadian Food Inspection Services (CFIA) before official submission of a safety dossier. These consultations can be formal or informal. Pre-submission consultations enable developers to obtain information on, for instance, the regulatory procedures, data requirements and data standards established by HC and CFIA.
In the USA, voluntary consultations with the FDA can take place at an early stage of product development, thereby giving developers the information on what safety issues may be relevant. From a business point of view, this is helpful as developers will get information on necessary safety tests, and also whether it is

[2] Under the US law, a food additive is any non-GRAS substance "the intended use of which results or may reasonably be expected to result – directly or indirectly – in its becoming a component or otherwise affecting the characteristic of any food", while under the European legislation, a food additive is "any substance not normally consumed as a food in itself and not normally used as a characteristic ingredient of food, whether or not it has nutritive value". In the USA, this means that novel (transgenic) proteins introduced in an organism can fall under the "food additive" annotation.

worthwhile to continue with the development of a product (Interview USA – FDA Annex 1.5). An additional benefit of these early consultations is that the FDA is aware of new developments.

An important advantage of enabling consultations with risk assessors at an early stage is that developers will be able get relevant information on safety and potential hazards. It can enable them to take precautionary measures if needed, adjust their research plan (e.g., by performing additional product checks related to a hazard), or to adjust their product design. Consultations with risk assessors or regulatory authorities have also benefits for the authorities, as they will be made aware of current developments in the field. This gives them the opportunity to anticipate upon developments, for example by gathering more information on or conduct research on new products and processes that may present a hazard.
Consultations together with stakeholder engagement are important in a Responsible Research and Innovation (RRI) approach, and similarly may be part of a Safe by Design strategy in product development. The main dimensions that comprise the backbone of RRI are anticipation, inclusiveness, reflexivity, and responsiveness (Stilgoe et al., 2013). Stakeholder engagement through consultation procedures and transparency may aid in the development of a new product, benefit public opinion and trust, as well as create value for users and society alike. Safe by Design is a way of working that implements the assessment of safety in all stages of development, rather than as something that only receives attention at the end of the product development (van der Berg et al., 2020).

For the EU, it might therefore be worthwhile to consider how consultation procedures may be included in the regulatory framework, if this is to be revised for NGTs. In all scenarios, early consultations could help developers to gain clear information on the appropriate regulations and the required data, in addition such early consultation may help to prevent safety issues and unwanted (side) effects.
In scenario B, this could entail consultation on what safety data is relevant for GMOs obtained with NGTs. In scenario C, consultations on what organisms and products may be excluded from regulatory requirements and what needs to be verified to ensure that an organism is excluded from regulatory requirements. In scenario D, consultations may include questions on the novelty of a trait and the potential hazards developers should consider.

Labelling regulations
In the EU, when a product is considered to be a GMO, this has consequences for both the approval process and for the labelling of products. Food products consisting of GMOs or containing >0.9% authorised GMOs must be labelled for consumers, in accordance with Regulation (EC) No 1829/2003. Labelling requirements are not the same everywhere in the world. In Canada, transgenic organisms have to be assessed for safety, but it is not mandatory to label products consisting of or containing these organisms.
In Japan, GM regulations dictate that foods from or with GMOs have to be labelled. However, these labelling requirements are not in place for GMOs with certain small edits, which are exempted from GM regulations (Interview Japan - OECD, Annex 1.3; Interview Japan – Nagoya University, Annex 1.4). Thus, in Japan food products from or with transgenic organisms are labelled, but food products from or with organisms with small genome edits are not.

Labelling of GMO products is an important attribute in the EU, as it gives consumers the choice to choose GMO-free food if wanted. Consumers may want to be able, due to (religious) believes or other considerations, to avoid NGT products altogether.

Costs of dossiers
A developer of a GMO food faces considerable costs for compiling a GMO safety dossier. The costs associated with adhering to the regulations for insect resistant corn have been estimated to be between 7.1 and 15.4 million US dollar, and for herbicide tolerant corn to be between and herbicide tolerant corn have been estimated to be between 6.2 and 14.5 million US dollar (Kalaitzandonakes et al., 2007). All costs involved in the regulatory science and registration when introducing a plant with a new biotechnology derived trait were estimated to be about 35.1 million US dollar in the period 2008-2012 (Philips McDougall, 2011). More recently, experts have estimated that the costs of bringing a genome edited crop to the market will be about 10.5 million US dollar when the crop is regulated as a conventional crop, and 24.5 million US dollar when it is regulated as a GM crop (Lassoued et al., 2019).

In addition, there are also costs involved for the government, which has to finance the assessment of the dossiers by the competent authority. In the EU, EFSA is responsible for the assessment of GMO dossiers, but also the member states give comments on the safety dossier that are submitted to the EFSA GMO Panel. These costs for compiling and assessing safety dossiers are not there for conventionally bred crops. Where there are large uncertainties of potential environmental or food safety risks, these costs for GMOs may appear justifiable. However, with the current NGTs, there are examples of organisms with minor edits that could have been achieved by conventional breeding, which would put into question the proportionality of regulatory compliance costs.
Alternatively, conventionally bred products may also have novel properties that need to be assessed under parallel legislation for novel foods.

There is international harmonization on safety assessment standards. The Codex Alimentarius has issued guidelines on how the food safety should be assessed of foods produced from GM plants, GM animals, and GM microorganisms.
These harmonisations ensure that the safety data obtained for authorization in one country, are transportable and also recognized in other nations. This limits the additional costs required for developers that want to market their products in more countries.
In practice, countries have "fast-track" approaches for GMOs that have been approved elsewhere, for example Paraguay, and Vietnam, where no further assessment of a GMO is needed if it is already assessed and approved in five other countries. African countries accept field trials performed in other countries. Also FSANZ has certain dossiers whereby the majority of previous conducted assessments from Canadian risk assessors. In the European Union, there is always a separate dossier review and judgement, whereby the dossier should fulfil all of the European requirements.

History of safe use
Since their first market introduction in the EU, transgenic GMOs used for food and feed have been subject to mandatory safety assessment. The first European legislation on GMOs was established in 1990, although national guidelines or legal frameworks had been adopted before. Although all mutagenesis techniques are considered as forms of genetic modification, even if they do not lead to DNA recombination (Case C-528/16), certain mutagenesis techniques are exempt from regulation because they have a long safety record (Annex IB of Directive 2001/18/EC, and Case C-528/16). These include chemical mutagenesis and mutagenesis by radiation, two methods applied before the GMO legislation came into force.
It raises a question if for novel techniques a history of safe use could be established at some point in the future, and if so, after which timeframe this could be done.
It is questionable if it is valid to continue using a cut-off date (which is relatively arbitrarily set) to determine safe use. Criteria to evaluate novel technologies and a way to establish when another technology may be considered safe in itself would be recommended. This is particularly the case since the trend for genomic technologies is that they become more precise with time, and that more knowledge on the techniques and the organisms that they are applied to becomes available (Interview Canada – HC, Annex 1.6).
For the application of novel techniques in plants, it is important to consider that they can be used in combination with other common procedures for plant breeding, such as backcrossing and selection. In plant breeding it is common to have selection procedures whereby off-types are discarded. These selection procedures may prevent that potential unintended, undesirable side effects are propagated and thereby do not end up in the final product. It is worthwhile to mention that there are differences between crops, whereby for certain crops such as maize, backcrossing is very common and easily achievable, while this is not true for other crops such as potato (tetraploid) and fruit crops (long time until flowering)
In product-based legislation such a question does not exists for techniques, although it could be a question if a certain trait (in a particular organism) can have a history of safe use.

There are various aspects of new technologies that should be assessed in order to gain insight into their safety. These include in-depth analyses at the molecular, biochemical and compositional level needed for products obtained with the new technology. In general, the European Commission highlights the case-by-case approach for safety assessment advocated by e.g., EFSA for site-directed nucleases 1-3, oligonucleotide-directed mutagenesis, and cisgenesis, indicating the need for updating current guidelines with relevant criteria (European Commision, 2021b).

There are differences in the way environmental and food safety are harmonized, whereby it tends to be more difficult to harmonize environmental safety in detail, due to the variability in receiving environments. This is the case for more traditional transgenic GMOs. Codex Alimentarius exists for the risk assessment of food products, but there is not a direct equivalent guidance for environmental safety evaluations. Potential environmental impacts are covered to some extent in the Cartagena Protocol, as well as in an OECD biology consensus document.

Animal breeding and microbial biotechnology sectors

The discussion on NGTs at the European level now focusses particularly on plants, yet implications for the animal breeding and industrial microbiology sectors are also relevant. In the EU legislation, the GMO legislation applies to all organisms, thus also micro-organisms, including fungi, and all types of animals. Nevertheless, these sectors differ considerably, which was observed in our earlier research and described in WFSR report 2021.506. One important distinction between micro-organisms and plants, which is also reflected in the current legislation, is that micro-organisms can be used in a closed system while plants, when cultivated, are in direct contact with the environment. Micro-organisms are (often) used under contained conditions in accordance with Directive 2009/41/EC, which means that there is no contact with the environment and the general population. Genetically modified micro-organisms can be used to produce other compounds, as long as the final product does not contain the production organism or recombinant DNA. Common mutagenesis practices with radiation or chemicals, that are exempt from GMO legislation, are applied in plants and micro-organisms, and combined with extensive selection processes. These mutagenesis techniques cannot be applied to introduce extra variation in animals, as there is a high probability that this will lead to many detrimental effects.

In addition, the breeding processes inherent to animal breeding make it necessary to introduce modifications in multiple animals for enabling propagation of the desired effect. The controversy surrounding the use of biotechnology in animals is larger than for plants, which in turn is larger than for microorganisms.

Such differences between plant, animal, and microbial sectors are important to consider in the process of regulatory changes. While discussions in the European context now focuses on plants, any consequential decisions may also influence the other sectors.

Conclusion

This report analyses the current regulation for GMOs in the EU (scenario A), a scenario with an adjusted risk assessment (scenario B), a scenario with an exemption for small genome edits, *i.e.,* SDN-1 and SDN-2, (scenario C), and a scenario with a product-based approach (scenario D), in light of the developments with NGT.

It is important to stress that in all scenarios the food safety can be safeguarded. From an enforcement point of view, given the difficulties with detection and in particular identification of small edits obtained with NGTs, scenario A and B pose difficulties and are less favoured. From this enforcement perspective, scenarios C (small edit exemption) and D (product-based) are more favoured. However, as indicated by the analyses of the scenarios, there are many other aspects related to all scenarios that should be considered as well.

For the application of NGTs, many safety-related arguments (environmental as well as food/feed safety-related) are brought forward, both by opponents and proponents. Nevertheless, many other considerations are also important, these include the co-existence with organic culture, consumer acceptance, the effect on innovation in general, and potential economic effects. Thereby it is necessary to make appropriate distinctions between the types of argument.

This report highlights various aspects and issues for the scenarios presented, which may guide decision makers in their deliberations on which scenario should be pursued within the EU. Such a judgement requires a careful weighing of all technical and safety-related aspects, but also socioeconomic aspects, which rests with the decision makers acting at the European community level.

References

DIRECTIVE 2009/41/EC OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 6 May 2009 on the contained use of genetically modified micro-organisms, (2009) (testimony of 2009/41/EC). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32009L0041&qid=1646820996699&from=NL

DIRECTIVE (EU) 2015/1535 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 9 September 2015 laying down a procedure for the provision of information in the field of technical regulations and of rules on Information Society services (codification), (testimony of 2015/1535/EU). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32015L1535&qid=1646822069742&from=NL

Cartagena Protocol on Biosafety. (2000). https://bch.cbd.int/protocol/text/

EFSA. (2019). *Special Eurobarometer Wave EB91.3 - Food safety in the EU*. https://doi.org/doi:10.2805/661752

EFSA GMO Panel. (2012). Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function. *EFSA Journal*, *10*(10), 2943. https://doi.org/10.2903/j.efsa.2012.2943.

EFSA GMO Panel. (2020). Applicability of the EFSA Opinion on site-directednucleases type 3 for the safety assessment of plants developed using site-directed nucleases type 1and 2 and oligonucleotide-directed mutagenesis. *EFSA Journal*, *18*(11), 6299. https://doi.org/doi.org/10.2903/j.efsa.2020.6299

ENGL. (2019). *Detection of food and feed plant products obtained by new mutagenesis techniques*. https://gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf

Eriksson, D., Custers, R., Edvardsson Björnberg, K., Hansson, S. O., Purnhagen, K., Qaim, M., Romeis, J., Schiemann, J., Schleissing, S., Tosun, J., & Visser, R. G. F. (2020). Options to Reform the European Union Legislation on GMOs: Scope and Definitions. *Trends in Biotechnology*, *38*(3), 231–234. https://doi.org/10.1016/J.TIBTECH.2019.12.002

European Commision. (2000). *Communication on the Precautionary Principle'*. https://op.europa.eu/nl/publication-detail/-/publication/21676661-a79f-4153-b984-aeb28f07c80a/language-en

European Commision. (2021a). *European Commission High-Level Event on New Genomic Techniques - "The Way Forward for Safe and Sustainable Innovation in the Agri-Food Sector"* (p. 29 November). https://ec.europa.eu/commission/commissioners/2019-2024/kyriakides/announcements/speech-commissioner-kyriakides-european-commission-high-level-event-new-genomic-techniques-way_en

European Commision. (2021b). *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*. https://ec.europa.eu/food/plants/genetically-modified-organisms/new-techniques-biotechnology/ec-study-new-genomic-techniques_en

Gaskell, G., Stares, S., Allansdottir, A., Allum, N., Castro, P., Esmer, Y., Fischler, C., Jackson, J., Kronberger, N., Hampel, J., Mejlgaard, N., Quintanilha, A., Rammer, A., Revuelta, G., Stoneman, P., Torgersen, H., & Wagner, W. (2010). *Europeans and biotechnology in 2010 - Winds of change?*

Gaskell, G., Stares, S., Allansdottir, A., Allum, N., Corchero, C., Fischler, C., Hampel, J., Jackson, J., Kronberger, N., Mejlgaard, N., Revuelta, G., Schreiner, C., Torgersen, H., & Wagner, W. (2006). *Special Eurobarometer Europeans and Biotechnology in 2005: Patterns and Trends*.

Jin, Y., Drabik, D., Heerink, N., & Wesseler, J. (2019). Getting an Imported GM Crop Approved in China. *Trends in Biotechnology*, *37*(6), 566–569. https://doi.org/10.1016/J.TIBTECH.2019.02.004/ATTACHMENT/3CC736BB-FB9B-487F-AD01-BFF9106E2EDA/MMC2.DOCX

Kalaitzandonakes, N., Alston, J. M., & Bradford, K. J. (2007). Compliance costs for regulatory approval of new biotech crops. *Nature Biotechnology*, *25*(5), 509–511. https://doi.org/10.1038/NBT0507-509

Kearns, P., Dima, O., Nowak, A., Napiórkowski, M., Magan, J., Nicolosi, M., & Widegren, E. (2021). *Re-Imagine Europa; White Paper on the Regulation of Genome Editing in Agriculture.* Task Force for Sustainable Agriculture and Innovation. Brussels. https://reimagine-europa.eu/publication/white-paper-on-the-regulation-of-genome-editing-in-agriculture

Lassoued, R., Phillips, P. W. B., Smyth, S. J., & Hesseln, H. (2019). Estimating the cost of regulating genome edited crops: expert judgment and overconfidence. *GM Crops & Food*, *10*(1), 44–62.

https://doi.org/10.1080/21645698.2019.1612689
Mampuys, R. (2021). *The Deadlock in European GM Crop Authorisations as a Wicked Problem by Design : A need for Repoliticisation of the Decision-making Process* [Erasmus University Rotterdam]. %09hdl.handle.net/1765/134194
McDougall, P. (2011). *No TitleThe Cost and Time Involved in the Discovery, Development and Authorisation of a New Plant Biotechnology Derived Trait*.
REGULATION (EC) No 1829/2003 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2003 on genetically modified food and feed, (testimony of No.1829/2003). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003R1829&qid=1646821091788&from=NL
REGULATION (EC) No 1830/2003 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL of 22 September 2003 concerning the traceability and labelling of genetically modified organisms and the traceability of food and feed products produced from genetically modified o, (testimony of No.1830/2003). https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32003R1830&qid=1646821164162&from=NL
OECD. (2021). *Consensus Documents: Work on the Safety of Novel Foods and Feeds: Plants*. Organisation for Economic Cooperation and Development. https://www.oecd.org/chemicalsafety/biotrack/consensus-document-for-work-on-safety-novel-and-foods-feeds-plants.htm
Parisi, C., & Rodriguez Cerezo, E. (2021). *Current and future market applications of new genomic techniques*. https://doi.org/doi:10.2760/0247
Purnhagen, K., & Wesseler, J. (2021). EU Regulation of New Plant Breeding Technologies and Their Possible Economic Implications for the EU and Beyond. *Applied Economic Perspectives and Policy*, *43*(4), 1621–1637. https://doi.org/10.1002/AEPP.13084
Stilgoe, J., Owen, R., & Macnaghten, P. (2013). Developing a framework for responsible innovation. *Research Policy*, *42*(9), 1568–1580. https://doi.org/10.1016/J.RESPOL.2013.05.008
Sturme, M. H. J., van der Berg, J. P., Bouwman, L. M. S., De Schrijver, A., de Maagd, R. A., Kleter, G. A., & Battaglia-de Wilde, E. (2022). Occurrence and Nature of Off-Target Modifications by CRISPR-Cas Genome Editing in Plants. *ACS Agricultural Science & Technology*. https://doi.org/10.1021/acsagscitech.1c00270
Sturme, M. H. J., Van Der Berg, J. P., Bouwman, L. M. S., De Schrijver, A., De Maagd, R. A., Kleter, G. A., & Battaglia-De Wilde, E. (2022). Occurrence and Nature of Off-Target Modifications by CRISPR-Cas Genome Editing in Plants. *ACS Agricultural Science & Technology*, acsagscitech.1c00270. https://doi.org/10.1021/ACSAGSCITECH.1C00270
Tsuda, M., Watanabe, K. N., & Ohsawa, R. (2019). Regulatory Status of Genome-Edited Organisms Under the Japanese Cartagena Act. *Frontiers in Bioengineering and Biotechnology*, *7*, 387. https://doi.org/10.3389/FBIOE.2019.00387/BIBTEX
Utomo, J. C., Hodgins, C. L., & Ro, D. K. (2021). Multiplex Genome Editing in Yeast by CRISPR/Cas9 - A Potent and Agile Tool to Reconstruct Complex Metabolic Pathways. *Frontiers in Plant Science*, *12*. https://doi.org/10.3389/FPLS.2021.719148
van der Berg, J. P., Bouwman, L. M. S., Battaglia, E., & Kleter, G. A. (2021). Future-Proofing EU Legislation for Genome-Edited Plants: Dutch Stakeholders' Views on Possible Ways Forward. In *Agronomy* (Vol. 11, Issue 7). https://doi.org/10.3390/agronomy11071331
van der Berg, J. P., Kleter, G. A., Battaglia, E., Bouwman, L. M. S., & Kok, E. J. (2020). Application of the safe-by-design concept in crop breeding innovation. *International Journal of Environmental Research and Public Health*. https://doi.org/10.3390/ijerph17176420
WFSR report 2021.506 Bouwman, L. M. S., Van der Berg, J. P., Battaglia E. & Kleter, G.A. (2021). Process-based versus product-based assessments of genetically modified plants, animals and micro-organisms (confidential report). Wageningen, Wageningen Food Safety Research.
Whelan, A. I., Gutti, P., & Lema, M. A. (2020). Gene Editing Regulation and Innovation Economics. *Frontiers in Bioengineering and Biotechnology*, *8*, 303. https://doi.org/10.3389/FBIOE.2020.00303/BIBTEX
Yang, N., Yan, L., Zheng, Z., Zhang, Y., Zhan, H., Tian, Y., Zhang, T., Li, R., Gong, X., Xu, M., Zhu, M., Wu, J., He, Y., & Zhao, Y. (2021). Editing gene families by CRISPR/Cas9: accelerating the isolation of multiple transgene-free null mutant combinations with much reduced labor-intensive analysis. *Plant Biotechnology Journal*, 1–3. https://doi.org/10.1111/PBI.13744

Annex 1 Reports interviews international experts

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Annex 1.1 Report on the interview Argentina

Date: 14/09 /2021
Organisation of the interviewee: Argentine Ministry of Agroindustry, Argentina
b National University of Quilmes, Argentina
Interviewers: [redacted] and [redacted]

General / Introduction

- What is the current legal framework for genome edited organisms, particularly for food and feed purposes

The discussion on the regulation for genome edited organisms started in 2012, because the perception was there that new products would advance the regulators' desk. In the next three years, there were discussions in the biosafety committee and public seminars; also input from stakeholders was collected.
The main clarification that was made is "when is an organism a GMO? " The definition of the Cartagena protocol was used, minus the word "living"). The biosafety discusses: 1) Was there use of a modern biotechnology (recombinant DNA) + OR nucelic acids into a cell, somehow during the process/, and 2) was there creation of novel genetic material.
So far, there were 25 decisions made on products.
Overall, the definition is quite clear. The part of the definition is whether there is recombinant DNA included. When there is a possibility that there is recombinant DNA in a product, this must be checked (*i.e.* there is an obligation to consult with the authorities).
An interesting case was a developer that used *Agrobacterium* for the modification of an ornamental plant. Analysis indicated that the WT contained *Agrobacterium* DNA, from a natural cause.

How is cisgenesis judged?
In most cases, cisgenic organisms will be considered a GMO by the commission. Also when there is another promoter (from the same species) in front of an indigenous gene, this is considered a novel combination of material.

How is SDN-3 judged?
In general, organisms obtained with SDN-3 will be a GMO, but there is an exception possible: This is a perfect allelic replacement. In case a different allele is transferred to the exact location in the genome, and not a novel combination of DNA.

Could you elaborate on the Biosafety committee: who are the members, and how many are there etc ?
The committee has about 50 members, from 20 organisation. In a meeting, on average 15 to 20 representatives are present. There are representatives from the different ministries (from health, environment, science ministries) and there are representatives from universities.
There are also private members, but these only have a voice, no vote.
Environmental organisations, were invited to join, but they didn't take place in the organisation.
The committee mainly has written communications with monthly meetings and also written decisions. These written communications are via a portal/webbased system.

- Do plants, microorganisms and animals all fall within this framework? Are there any distinctions made between them?

The legislation and the procedures involved are for plants, microorganisms, and animals. The same laws apply, independent of the biological Kingdom to which the organism belongs.
For microorganisms, there have been very few examples with genome editing here. Mainly used as a negative selection tool.

- What are the main strenghts of the legal framework, and what opportunities does it give?

Main strength: the use of the Cartagena protocol definition, which is internationally recognized.
Processes in Argentina are fully compatible with the protocol. This has as the main advantage that other

countries can analyse organisms in the same way.
This is in contrast with, for example the USA, where there is a system with early decisions. There are huge difference in how transgenic rules apply, for example there are differences in types of organisms. Despite the early decisions, rules are still unclear because of the differences.
Another strength is that the framework is not a list of (existing) techniques. The definition and processes can also be used to determine whether an organism is GMO for novel techniques (that will be developed in the future.
In practice: in 60 days there is a decision on the question: "is an organism GMO or not?"; or there is the outcome that there is not sufficient information. Decisions are made, and the decision making is relatively quickly.

We control all new varieties (also from other breeding methods). When there is a trigger, there can be a risk assessment for products with a new trait, thus also when the new variety is not GMO (*i.e.* a trait-based trigger, in which case it is the hazard that is the trigger of the assessment under conventional laws, as in the case of cucurbits with altered levels of glycoalkaloids notified for variety registration, which alerted regulators). A regulator can start a risk assessment process around a risk hypothesis. An example was the presentation of a sorghum with increased levels of cyanide, a variety used for cleaning soil of nematodes.
Regulator has a situation in place: committee which decides that there is a risk hypothesis. The conventional regulator states that when there is a risk of crossing with wild relatives: approval under the condition that there is separation between crop and wild plants.
Thus, also if a new product/organism is not a GMO, there can still be a risk hypothesis and then there is a safety assessment. "To mind the gap" between GMO's and non-GMO's.
The possibility to have a preliminary consultation: before a (final) product is obtained.
Biosafety commission can react. Data has to be submitted for the real decision when a product is obtained.
The preliminary outcome can be used for, for example, project proposals, investments etc. (for example, it may be easier to get support for funding after the preliminary consultation has been completed). The final risk assessment sill still require full data.

- What are the main weaknesses of the legal framework, and what threats do you see?

Menace from the outside: if customers (i.e. countries where products are sold) do not use the same rules, (f.e. China, EU). This can be a problem, because not all the data required in other countries will be available for some products, which may lead to trade issues.
For GMO there is an extra question: on fit for export? GMOs for expert from Argentina are mainly products from multinationals, with worldwide markets, that can be sold everywhere. Examples are soybean with herbicide tolerance or maize, as well as meat animals.
Smaller players are exploring niche products: f.e. only for in Argentina, or for neighbouring countries that have similar rules. Often no worries, because it is not a main export product.

Definitions and scope of the regulation

- What is the definition used in legislation? Is the definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

The definition of the Cartagena protocol, minus the word "living" word living

Added as background:
g) "Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;
(h) "Living organism" means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids;
(i) "Modern biotechnology" means the application of:
a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
b. Fusion of cells beyond the taxonomic family, that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection;

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?
  - *Examples are: siRNA, modification of epigenome*

Everything can be discussed under this definition to see if it qualifies as GMO.
There can be debate of when a combination of DNA can be considered novel. If an organism is not a GMO, that we can still regulate it, based on a risk hypothesis. This trait-based trigger is a bit like novel trait in Canada.
Currently, the main developments in biotechnology, such as synthetic biology and gene drives, and all other examples of which I am familiar are GMOs under the definition.

  - *Mutation is the same as one that occurs naturally? Is that inherently considered safe?*

In strict terms, it doesn't play a role.
However, the question "is the same mutation already on the market somehow" is asked and considered by the commission. For now, mutations that are introduced are often also seen in nature / in other varieties. The fact that the mutation is already present, is usually to illustrate the familiarity, which in general leads to trust in the mutation.

- What is the view on unintended effects of genome editing techniques?

Focus: on the determination if something is GMO or not, which includes all changes that are made.
Producers must assess every potential off target sites, also to verify that there is no unintended integration of foreign DNA in these locations. Knowledge in the potential off target locations can be used for further assessment. If every off target site should be sequenced, then there is information if there is any risk on these state.

Consultation possibilities (e.g. for developers to consult risk assessors / regulators)

- How is your experience with consultation?

See Above

- Could you comment on the outcomes of the consultations so far?

See Above

- What feedback, if any, has there been from applicants, risk assessors, and regulators about their experience with the consultation procedure?

See Above

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" GMO's and from conventionally obtained organisms (f.e. via mutagenesis breeding)?

Not specifically discussed

- What risk assessments are carried out? Does it cover food and environmental safety?

See above

- Unintended effects: how are these taken into account in risk assessment?

Food and feed (safety) and environmental aspects are considered together.
The biosafety Commission decides for whole system: if it is GMO.
A commercial impact assessment is only done for GMOs. The assessment and relevance of possible off-target effects of gene editing is explained in another publication. Potential off-target sites will be checked for (besides the assurance whether it is a GMO or not)

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from internal market, as well as imported products)?

There are no labelling requirements for commercial GMOs.
Only for seeds there is an obligation to label if they are GMO, so organic producers do not get confused, and

make claims later. Besides legal provisions, there are private systems in place which may have different interpretations.

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of GMO/Genome editing regulations?

Not specifically addressed

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to worldwide)

See above

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country?

There is no opposition from the public towards biotech in general. NGOs are also not very outspoken on GMO in Argentina. They do not work or advertise on the use of GMOs or with genome editing, but there is limited negative propaganda. NGOs are worried about the use of glyphosate and campaign against that.
In general, there is an implicit trust to the regulators. If you would ask on the street if people would want to eat GMO food, they are likely to say no, but there is no general worry or action on that front. There is no opposition from the public, whilst there is a lot of noise surrounding one of the herbicides associated with GM crops (glyphosate). There have been no major food scares either.
An example to illustrate this attitude, can be found in the first GMO crop that was entirely developed in Argentina. This crop was presented with proud by the Argentinian president to the whole country. Even with this maximum exposure to the Argentinian public, only one concerned response was received.
Public supports the local science.

- Is there a different feeling towards genome editing and other new GM techniques?

Not specifically addressed

- What is likely the cause of this general view/or different views?

Not specifically addressed

- How is public perception the regulation?

Not specifically addressed

International harmonization:

- What aspects should be harmonized internationally in your opinion?

All customers are parties in the Cartagena protocol, while Argentina is not. In practice, this means that in order to export products, Argentina has to act in line with the protocol, for example the " may contain" document, as in article 18 of the protocol, has to go with a shipment.
It should be granted that the definition of GM is clear and recognized everywhere. Discussions on what is a novel combination will remain.

- *Does your government strive towards international harmonization?*

Not specifically addressed

Annex 1.2 Report interview Australia

Date: 19/10/2021
Organisation of the interviewee: Food Standards Austalia New Zealand (FSANZ)
Interviewers: and

Additional comments from interviewers are given in *black italic*; answers are given in blue.

General / Introduction

- What is the current legal framework for genome edited organisms, particularly for food and feed purposes?

One of the key things from regulatory point of view is that there are separate legal frameworks for GM food products and for GM organisms. The definitions are not shared.
In practice, what is regulated as GM Food pretty much aligns with what is considered a GM Organism.

Q: How do foods from genome editing techniques in this framework?
There can be ambiguity of what modifications (e.g. gene edits) fall under the definition of "gene technology". There have been no examples so far, and no cases brought to court, which could provide more clarity on the interpretation of definitions. As far as we know, there are no products on the market on the moment, and no need for enforcement.
The agency has had conversations with companies that develop products.

Q: Could you tell more about these conversations and consultations?
In general, we encourage consultations: to have early and frequent conversations with FSANZ to request where a new product belongs in food regulations. There is currently no mandatory consultation, but only a voluntary arrangement. It is desirable to have such a mandatory system, though, also because oversight is wanted by society and offers scope for innovation.

- Do plants, microorganisms and animals all fall within this framework? Are there any distinctions made between them?

They are all treated the same, but so far there is only experience with plants and micro- organisms. There are no expectations for gene technology in animals for the coming years.

- What are the main strenghts of the legal framework, and what opportunities does it give?

Stakeholders (regulated community): they appreciate the predictability of the framework. This is not only in the regulations, but especially the predictability in the assessment processes.

- What are the main weaknesses of the legal framework, and what threats do you see?

Firstly, there is a an issue with the definitions. We are currently in the process of reviewing and revising definitions. The current definitions are considered not fit for purpose, outdated and unclear.
Besides, there is a lack of proportionality. With the process-based definition, every product from genetic technologies is scrutinized in much detail, but this is not in proportion to the (food safety) risk these products pose. The current approach may have been justified 25 years ago, because of uncertainty with new technologies, but not anymore. The government is spending a lot of money on assessing products with very low risk. In addition, the procedures also pose large financial burdens for companies.

Definitions and scope of the regulation

- What is the definition used in legislation? Is the definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

See above.

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?
  - *Q: for example: epigenome editing.*

I expect that epigenome editing is covered. It is the question if we want to regulate this type of biotechnology.

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" GMO's and from conventionally obtained organisms (f.e. via mutagenesis breeding)?

In our current work on revising definitions, we particularly consider the nature of the modifications that are made using gene editing. These types of modifications from gene editing are compared with the modifications created with other, conventional techniques, genetic modification, and natural & spontaneous mutations. As part of the assessment, we have found no different risks from genome editing compared to conventional breeding. This conclusion also includes off target effects. This points towards their possible exclusion under revisions to the legislation.
(Mutagenesis techniques are considered to be conventional breeding techniques).

- What risk assessments are carried out? Does it cover food and environmental safety?

See above

- Unintended effects: how are these taken into account in risk assessment?

See above.

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from internal market, as well as imported products)?

In Australia, there is mandatory labelling of GM foods: any food produced with GM technology. Labelling is on a product-based basis: a product has to be labelled if it contains modified DNA or modified protein, or when the characteristics of the products have been altered.
There is a practical limitation, which is for food prepared for immediate consumption, similar to exemptions for conventional foods.

Q: is there any threshold for labelling, f.e. a minimum percentage?
No there is not. If you can show that there is a GM product in a food, it has to be labelled. The labelling threshold only applies to the unintended presence of approved GMO-derived components.

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of GMO/Genome editing regulations?

This is one of the issues that we consider for revising regulations, is the equivalence to conventional products.
Our primary considerations are risk considerations, of products made with new technologies compared to those with conventional methods.
In addition, there is the consideration that one must be able to tell regulated and not regulated products apart.

With regards to labelling, requirements will not be changed. In general, these types of products would not have new DNA or new proteins, or altered characteristics. Any exclusion from GM legislation applies to products that would not trigger labelling.

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to worldwide)

Current regulations: do very little for innovation, a shared problem worldwide.
Particular for small and medium sized players it is very difficult to innovate, as it is very costly to get a

regulatory dossier. There may be innovative ideas, but they will not be translated into products. We have had no such applications ever.
The effect on innovation is an additional benefit that may follow from the proposed changes in legislation; it is not a primary driver. We want to acknowledge effect on innovation. There may be a benefit from a more proportionate approach.
The situation around labelling is particularly stifling. Many manufacturers actively avoid GM products and ingredients. So they do not have to label the products.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country?

This is a very timely question, as we just completed some consumer research. This consisted of a literature review, with primary view on Australia and New Zealand, and of focus group research. There is possibly a slightly more positive attitude among consumers towards genome editing compared to transgenic techniques, but this is not stark.
Consumers still have a very different feeling towards conventional methods and genetic techniques. When you spend time to discuss the matters and really go into detail it is clear that people feel more positive about changing existing genes rather than introducing new genetic material. The reactions to some specific examples were very positive, for example when it comes to welfare traits for animals. The SLICK trait for heat tolerance in livestock was received well, as this is quite relevant for Australian livestock producers. (Semen of SLICK cattle has been imported in order to test if the trait could be relevant in the Australian climate.)
Also other applications were positively received, for example to improve drought tolerance.

- Is there a different feeling towards genome editing and other new GM techniques?

See above

- What is likely the cause of this general view/or different views?

The situation you describe is quite similar to what we see in Europe, where the societal aspects and the questions on power in the food chain are important to consumers.
Consumers do not consider the innovations separately, but always consider them as a part of the entire (food) system. There are many considerations, not just safety considerations (although that is one of the conditions for use they set). The perceived societal benefits of such traits colour the views of the public, which also wants proper regulation.

We discussed with an expert from South America about the consultation required there.
Would love to have a system to be able to do that. At the moment there are only voluntary arrangements for consultations in Australia; at least until primary regulations are changed.
It seems society wants to have some form of oversight, which could be created by such a system. In addition, it enables clarifying the scope for innovation.

- How is public perception the regulation?

See above

International harmonization:

- What aspects should be harmonized internationally in your opinion?

Currently, there is a high degree of harmonisation in assessment of GM products.
I have lower expectations of what may be possible for new breeding technologies, as different approaches to regulate these techniques are emerging worldwide. They are not vastly different, but still rather different. Some countries will not assess products created with new technologies at all, as they are out of scope of regulations.
International harmonisation is obviously preferable, not just for safety assessment, but also to facilitate trade between countries – but it is questionable to what extend harmonisation is achievable with the new techniques.

Q: You have collaboration with Health Canada: what spills over from there?
There is some overlap with the propositions for regulatory improvements we make, but not completely

aligned with Canada. In general, we are very likeminded. There is sharing of resources and expertise in this area.
Overall, the developments and discussions surrounding the regulation of genome editing techniques are quite different from those with the " old" GM techniques (in the 80s and 90s).

- Does your government strive towards international harmonization?

See above.

Others

Q: While food standards are the same, environmental regulations are different between New Zealand and Australia, correct?

Indeed. There is a Joint food standard between the two countries, but environmental regulations are different between Australia and New Zealand.
FSANZ is located in Canberra and Wellington. FSANZ also receives funding from New Zealand, but it is an Australian governmental organisation.

Annex 1.3 Report interview Japan (OECD)

Date: 21/10/2021
Organisation of the interviewee: Organisation for Economic Development (OECD) representing Japan
Interviewers: [redacted] and [redacted]

Additional comments from interviewers are given in *black italic*; answers are given in blue.
Nb. A presentation was provided by the interviewee on the regulatory framework. The information from this presentation + extra information given is here below.

General / Introduction

• What is the current legal framework for genome edited organisms, particularly for food and feed purposes?

Various governmental institutions are involved in the regulation of GMOs in Japan, with differences for Environmental safety, food safety and feed safety. An overview of the regulatory authorities:

- Environmental safety:
  - Ministry of Environment (MOE)
  - Ministry of Education, Culture, Sports, Science and Technology (MEXT)
  - Ministry of Agriculture, Forestry and Fisheries (MAFF)
  - Ministry of Economy, Trade and Industry (METI)
  - Ministry of Health, Labour and Welfare (MHLW)
  - Ministry of Finance (MOF)
- Food Safety:
  - MHLW (risk management)
  - Food Safety Committee (FSC) (risk assessment)
- Feed Safety:
  - MAFF (risk management)
  - FSC (risk assessment)
- Food Labelling:
  - Consumer Affairs Agency (CAA)

The regulatory framework:

- Environmental safety:
  - The Cartagena Act
  - "Type 1 use" (under open system) needs approval by competent ministries based on risk assessments.
  - https://www.biodic.go.jp/bch/english/cartagena/index.html
- Food Safety:
  - Food Sanitation Act
  - GM foods need approval by MHLW based on risk assessment by FSC.
  - https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/shokuhin/idenshi/index_00002.html
- Feed Safety:
  - Feed Safety Act
  - GM feeds need approval by MAFF based on risk assessment by FSC.
  - http://www.famic.go.jp/ffis/feed/r_safety/r_feeds_safety.html
    For food and feed safety: a combined with scientific risk assessment from Food safety commision FSC (roughly comparable to the EFSA in Europe).

See below for definitions

Notifications to the competent ministries are required for new genome edited organisms, also when they do not fall under GMO legislation(see definition for criteria).
For the environmental safety of genome edited organisms, the following information is needed: a) The fact that the organism does not possess remnants of extracellularly processed nucleic acid or its replicated

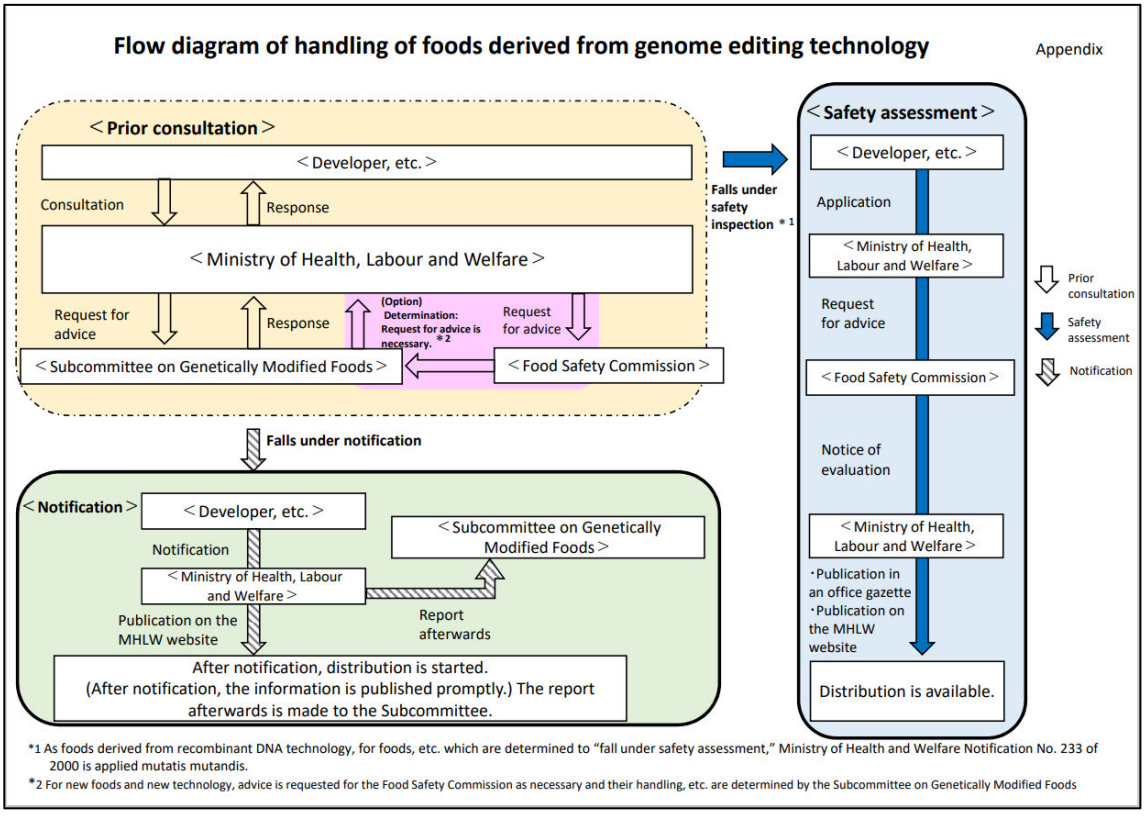
product b) Taxonomical species of the modified organism, c) Method of genome editing used for the modification d) Modified gene and its functions, e) Change of traits added by the modification. F) Changes of traits other than those described in e), if any g) Usage of the organism, h) Discussion on possible influences on biological diversity when the organism is used.
The information in this notification is a bit simpler than what is needed for GMOs.

For food safety, slightly different rules occur. Genome edited foods (SDN-1 and some of SDN-2) still need notification to MHLW with information below.
a) Names of item and breed and summary (usage and intended use) of the developed food, b) Method of genome editing technology used and details of modification, c) Information on confirmation that there are no remaining foreign genes or their parts, d) Information on confirmation that confirmed changes in DNA do not cause production of new allergens having adverse effects on human health or increase of known toxic substances contained, e) For items in which modification affecting the metabolic system was performed in order to increase or decrease specific components, information on changes in major components (nutrient components only) related to the target metabolic system, f) Year and month of marketing (*Notify the MHLW of it after marketing)

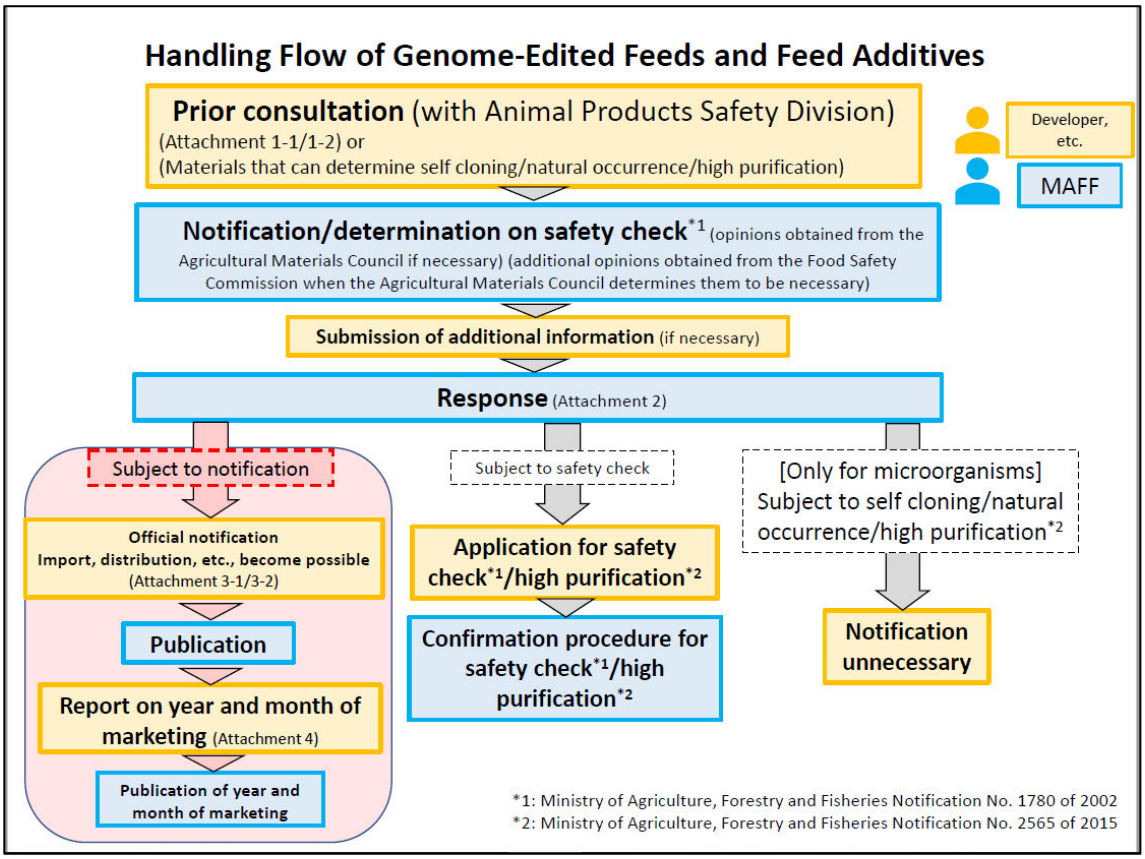
Information that has to be given for genome edited feeds is almost same as that of genome edited foods, with the exception for allergens and adverse effects of human health, and the ministry whereto to report.

There is a system in place of consultation for genome edited foods. This consultation should be done prior to a notification. Applicants will submit their application to the Ministry of Health, which will request an expert group meeting from the Food safety commission in order to have it confirmed that is not a GMO, and to enquire about the safety.
If confirmed, the applicant can then proceed to sending its notification to the ministry in order to make it official. The outcome of the prior consultation can also be that a safety assessment is needed.

The Consultation procedure, strictly speaking, is voluntary. Although the notification is therefore not completely mandatory, it is still strongly recommended.



The procedure for consultation is similar for Genome edited feeds:



To what extend do the different Japanse organisation try to harmonize amongst themselves?
There are meetings between the different ministries involved, with risk assessors, in order to harmonize rules and decisions. For genome editing, the timing of the decisions was harmonised.

- Do plants, microorganisms and animals all fall within this framework? Are there any distinctions made between them?

Frameworks differ for environmental safety, food and feed safety – not for types of organisms. (see above)

- What are the main strenghts of the legal framework, and what opportunities does it give?

Enforceability of the regulations. Products derived from exempted techniques are not distinguishable from products derived from conventional ones.

- What are the main weaknesses of the legal framework, and what threats do you see?

For example the definition for when SDN-2 is considered a GMO and when not*, is that clear enough?*
(See definition for introduction on this topic)
The rule itself is not so clear as, for example, the criterion "several bases" is not concrete. Once an applicant has started the consultation, it can be clarified what can be considered "several bases", thus it can be clear for new genome edited foods or crops.
The expectation is that developers will focus on using SDN-1 when possible, as it is not easy to state when SDN-2 is regulated as a GMO.

Definitions and scope of the regulation

- What is the definition used in legislation? Is the definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

The definition of GMOs differ are as follows.
- Environmental safety:
  - 'LMO' in the Cartagena Act

    - An organism that possesses nucleic acid, or a replicated product thereof, obtained through use of the any of the following technologies.
    - (i) processing of nucleic acid extracellularly
    - (ii) fusion of cells of organisms belonging to different taxonomical families
- Food safety:
  - 'GM foods' in an announcement by MHLW
    - Foods derived from or containing organisms produced by recombinant DNA techniques
- Feed safety
  - 'GM feeds' in an announcement by MAFF
    - Feeds derived from or containing organisms produced by recombinant DNA techniques

for Genome edited organisms:
- Environmental safety:
  - A notification by MOE (Feb. 2019)
  - If an organism does not hold nucleic acids processed extracellularly (SDN-1), it is not regulated under the Cartagena Act.
  - Organisms produced by SDN-2 and SDN-3 are regulated as GMOs.
  - https://www.biodic.go.jp/bch/download/genome/genome_chirashi_english.pdf

If CRISPR-Cas is used in the process, but removed in the end product (no newly expressed protein or recombinant DNA present), the end product is NOT considered a GMO.
Rules and definitions are slightly different food and feed safety.
- Food safety:
  - A decision by MLHW (Sep. 2019)
  - https://www.mhlw.go.jp/stf/seisakunitsuite/bunya/kenkou_iryou/shokuhin/bio/genomed/index_00012.html
    - Foods derived by SDN-1 will not be regulated under the Food Safety Act if there is no transgene remained.
    - Foods derived by SDN-2 will not be regulated
      - if there is no transgene remained, and
      - if the change is deletion of bases, or substitution or insertion of several bases.
    - Foods derived by SDN-2 will be regulated if they do not correspond to the conditions above.
    - Foods derived by SND-3 will be regulated.
- Feed safety:
  - An announcement by MAFF (Feb. 2020)
  - https://www.maff.go.jp/e/policies/ap_health/petfood/

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?

Various new applications are being developed by the national agricultural research organization

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" GMO's and from conventionally obtained organisms (f.e. via mutagenesis breeding)?

Not specifically addressed

- What risk assessments are carried out? Does it cover food and environmental safety?

See above

- Unintended effects: how are these taken into account in risk assessment?

The focus of the scientific assessment is on the target effects.

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from internal market, as well as imported products)?

- Regulatory authority: Consumer Affairs Agency
- Relevant acts:
  - Food Sanitation Act
  - Act for Standardization and Proper Labeling of Agricultural and Forestry Products
- Mandatory labelling
  - GM foods (under certain handling conditions)
  - GM foods not segregated
- Voluntary labelling
  - Non-GM foods (under certain handling conditions)*
- Exception
  - GM labelling is not mandatory for products that do not contain any GMO-related recombinant DNA or newly expressed protein anymore, including highly refined products such as oil, soy sauce, starch etc.
- https://www.caa.go.jp/en/policy/food_labeling/pdf/syokuhin736.pdf

*No labelling is needed when no newly expressed protein or recombinant DNA is present. Ability to enforce the legislation is important here

No mandatory labelling of genome edited foods
- It is impossible to distinguish foods derived by genome editing and those derived by conventional breeding, if no transgene is remained.
- Systems to track genome edited foods are still insufficient.
- At the same time, the agency recognizes consumers' opinion requesting labelling that enables selection.

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of GMO/Genome editing regulations?

They are detectable: recombinant DNA or newly expressed protein present to be a GMO / GMO food.

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to worldwide)

Not easy to make it clear. There is a relationship between the new policy and innovation.
The Japanese government wanted to invest in genome editing organisms and crops. Before the new regulations came into force, there were no clear rules, which was considered to hamper innovation.
Advisors made a report on how to move forward, which stated that clear rules must be in place, which could also promote innovation. Next, the different ministries made these rules (see above).

Would you see Japan is moving to a more product-based approach?
-Difficult to answer this question precisely. In the basis, the approach is still process-based, whereby SDN-1, SDN-2, and SDN-3 categories are major determinants. The risk assessment in the regulatory system is done on a product-based basis. This is largely the same as with GMO regulations.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country?

Concerns are expressed from NGOs, but it is not sure if these concerns represent what the majority of the consumers feel. There are certain supermarkets and companies that state they will not sell or use genome editing products.

- Is there a different feeling towards genome editing and other new GM techniques?

Not specifically addressed.

- What is likely the cause of this general view/or different views?

Not specifically addressed.

- How is public perception the regulation?

Not specifically addressed.

International harmonization:

- What aspects should be harmonized internationally in your opinion?

Not specifically addressed.

- Does your government strive towards international harmonization?

At the moment, the Japanese government is not active in promoting in harmonisation for regulation of genome edited organisms in an international context. Although they are in favour of harmonisation, they are not actively pursuing it. Japan has set their own rules, it will be difficult to have these rules in other countries.

The ministry of Agriculture is working on genome editing crops and there is governmental funded research on genome edited crops. There is the intention to market these crops, but it will take time before this will be in practice.
In many countries, opposition from consumers and NGO leads to the abandonment of funding of GM research.
There is fear that there is misunderstanding from the public: that it is perceived that regulatory frameworks are only made for developers and to help innovation.

Discussion of two recent examples of genome edited products from Japan

Tomato with increased GABA

- Sanatech Seed Co., Ltd. (a venture company from Tsukuba Univ.)
- Knock-out of the *glutamate decarboxylase* gene, resulting in increased γ-aminobutyric acid (GABA)
- CRISPR/Cas9 gene was introduced using the Agrobacterium vector, and then its absence was confirmed in the genome of offspring.
- Dec. 2020: Notification to MAFF (cultivation and feed) and MHLW (food)
- May 2021: Distribution of seedlings free of charge for home gardeners
- Sep. 2021: Start selling fruits
- Oct. 2021: Start selling seedlings for home gardeners

Are the tomatoes sold with health claim / advertisement for higher GABA content?
Not to the knowledge of the interviewee.

Increased-fillet sea bream

- Regional Fish Institute, Ltd. (a venture company from Kyoto Univ. etc.)
- Knock-out of the *myostatin* gene, resulting in increased muscle
- CRISPR/Cas9 mRNA was injected into eggs, and then its absence was confirmed in the genome of offspring.
- Sep. 2021: Notification to MAFF (cultivation and feed) and MHLW (food)
- Oct. 2021: Distribution of fillets through a crowdfund platform

The two applicants (for the fish and the tomato) are quite different from large biotech. What is general trend?
There is no information on this at the moment.

Annex 1.4 Report interview Japan (Nagoya University)

Date: 27/10/2021
Organisation of the interviewee: Nagoya university, Japan
Interviewers: [redacted] and [redacted]

Additional comments from interviewers are given in *black italic*; answers are given in blue.
Nb. Preliminary answers and background information were provided by the interviewee. This information has been used for this report.

General / Introduction

- What is the current situation in Japan for new biotechnologies such as gene editing? For example, is there a dialogue within society on the use of gene editing?

Many workshops and seminars are held, sometimes including a member from consumer organisation. Most of these meetings are organised by university employees, such as professors and researchers; some are organised by the anti-GMO movement.
There were no major events, such as consensus conference, public dialogues so far.

Genome editing considered as GM technique by Japanese NGOs. There is campaigning from anti-GM groups against genome editing. In Japan, there have been groups against GM for 20 years.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotechnology in your country?

Recently, there have been opinion surveys and focus groups. It seems that the general public does not see any difference GM and genome editing: they are both considered to be manipulation of DNA. The general feeling among the public is that it is very complicated material, not easy to understand.
The major concerns are for: food safely; not environmental safety nor animal welfare.

There have been a number of incidents in the past with safety, that are likely to be underneath the safety concerns. There was the incident with the nuclear power plant of Fukushima 10 years ago. About 20 years ago, there were incidents with BSE. About 40 years ago, there were incidents with heavy metal contamination (mercury) in fish, which led to many cases of illness (~ 10.000 people), and to disformed babies, due to disturbed development.

Yearly, the Food Safety commission of the makes a ranking of the food safety concerns amongst consumers. There, GM food does not score high (See additional material).

- Is there a different feeling towards genome editing and other new GM techniques?

Based on my experience of focus group interviews: general public do not differentiate gene editing and transgenic techniques. since both are manipulating DNA

- How were the genome-edited GABA tomato and red bream fish received by consumers?

As for tomato, well accepted. Difficult to tell for fish (red bream) [very limited amount]
Consumers groups are active to criticize by collecting signatures and petitions to government. The mass media has not given major reactions, compared to the case of GMO.
Both the tomato and the fish are not sold in supermarket, but they are sold from developer to consumer. For the tomatoes, distribution was well organised and there was quite a lot of interest. 4000 Seedlings of the tomato (to be planted in gardens) were sold quickly.
The first sales of tomatoes themselves have started, but the results are not known yet.
The mass media touched upon the tomatoes issue with a warm heart, not criticizing it.
The tomato was created by Sanatech Seed Co. (Univ of Tsukuba + Corteva startup)
The gene-edited sea bream fish has been created by company Regional Fish Co. (Kyoto University and Kinki

University spin-off & start-up) and its product is distributed amongst the crowd funders who funded its development
The Intellectual property rights are quite different for both products. For the tomato, it has one window to negotiate with patentholders. For the fish, there are two patentholders, meaning there is not one window for negotiations. Then there are general IP issues with CRISPR-Cas technologies, that have to be solved before the fish can be sold.

Additional explanation on the IP issues, received via email on 30 October 2021:
As far as I understand, the Corteva (former Dow-Dupont) has kindly established an unified window to negotiate terms and conditions of using patents of CRISPR/Cas9. As you know, the IP issue of CRISPR/Cas9 is still under the lawsuits between the UC Berkeley, and Broad Institute (Harvard University). Also another university from Lithuania is involved regarding the scope of patent. The situation is quite complicated and very difficult for developers deciding who to negotiate to get license to use the technology. In this respect, the Corteva decided to negotiate all patent holders as one stop middleperson for users who want to apply this technology. But this Corteva's business is only for "plant", not animal, nor microorganism. For this reason, the Japanese Sanatech Seed, the developer of the high GABA tomato, had faced with little problem regarding the IP issue compared with the Regional Fish who developed gene-edited fish. The Regional Fish needs to negotiate two or three patent holders at the same time before place their product on the market. This seems to take time, and this is the reason why they have not actually started "selling" their fish. They just give their fish to limited number (231 people so far) of persons in exchange of crowd funding.
The Regional Fish has successfully notified their second product "Torafugu" (a kind of blowfish) on 29 November. The fish is characterized as fast growing. In total, there are three gene-edited products which were notified to the government in Japan.

- Would the public feel differently about the use of gene editing in plants, microorganisms, or animals, or is it all the same to them?

Based on consumer survey research, there is some difference between plants and animals as regards acceptance. Please refer to the following article. As for microorganisms, I have no idea.

Kato-Nitta, N. et al. (2021) Effects of information on consumer attitudes towards gene-edited foods: a comparison between livestock and vegetables, CABI Agriculture and Bioscience
https://doi.org/10.1186/s43170-021-00029-8

There has not been a survey for the feeling towards fish, in the research tomato and pig were compared. Pig was chosen as there is research with genome editing in pigs, for example into PRRSV resistance. The outcome of the survey is that consumers are less willing to eat a genome-edited pig than a genome edited plant. The main concern from the public is about edits that result in an increase in the size of the organism (both for plant and for animals).

- Is there a difference between gene editing applied to food & agriculture compared with, for example, use for medicinal purposes (human health) or production of other non-food compounds such as bio-fuels and bio-polymers?

I do not have any evidence related to gene editing, but mostly consumers tend to accept medical applications and industrial applications, as far as the products are not food.

- What is likely the cause of this general view or difference in views?

Japanese consumers seem to be very sensitive to food safety issues (see above for explanation).

- How is the public perception of the regulations?

Consumers always express their opinion that they prefer to have right to choose. In this respect, labelling plays a big role. But no labelling is needed for gene edited products in Japan. The survey result shows that the Japanese public prefers to have strict regulation and labelling on gene edited products.
I have no information regarding how the public evaluate the newly introduced guidelines of gene edited products, but based on the previous surveys, Japanese consumers would not be very satisfied with the current regulations of gene edited products.

The public at large may not be much aware of the guidance for gene-edited organisms, as no legislation has actually been changed and the target audience for these guidelines are the institutions and ministerial departments. The authorities maintain a low profile on this matter.

Consumer agencies in Japan are stimulating food producers to give information on products. For both products that are now on the market, it is expressed that the product is gene edited. It is not guaranteed that this will be the case for genome edited products that will be brought to the market in the future. Japanese consumers prefer the right to choose.

At the moment, there is a movement from NGOs with regards to labelling: they are collecting signatures for a petition. They want a mandatory safety assessment and labelling of genome edited food products. There is no concrete result from this initiative yet, and no response from the authorities.

Policy context

- How does innovation policy in Japan affect the policy on gene editing in particular, and biotechnology in general?

Japanese Integrated Innovation Policy (2018) adopted by the Cabinet has greatly affect the policy on gene editing. It has set the deadline for Japanese competent authorities to conclude on the regulatory status of gene edited products. In the following year, Biotech Strategy 2019 was published by the Cabinet Office and the Strategy is being updated annually. The Biotech Strategy covers diverse areas related to bioeconomy, not just gene editing.

The use of and innovation with genome editing, is a wish from the authorities, a top-down order so to say. Since the EU JRC has published the report on new breeding techniques in 2011, the Japanese authorities started to collect information. After that collection of information.

Since then, progress has been made with development of a policy. There is no new legislation implemented, but low-profile guidance documents have been published. The public is not very aware of the changes, and they have not been discussed in parliament. Experts and bureaucrats (policy employees) made the decisions. The opinions of some stakeholders, such as producers and NGOs, have been asked for.

- More generally, how important is biotechnology considered to be important for the Japanese economy, now and in the future?

Current government seems to regard biotechnology is one of the key areas of innovation, and bioeconomy is a major concept here. However, public spending on R&D and education is declining and very low level compared with other OECD countries, which weakens the competitive strength. This is what many Japanese researchers have as their overall impression.

International context:

- What influence does the approach followed by other, foreign countries have on the views and approaches taken by Japanese stakeholders?

Usually, the Japanese government tends to watch US and EU policy development before drawing conclusions on regulatory issues. As for gene editing regulation, the existing GM regulation makes it difficult to adopt other countries' approaches directly. However, the Japanese government has paid much attention to other countries' regulatory developments, such as EU-JRC reports.

- What aspects could be harmonized internationally in your opinion?

Transparency (disclosure of product which had gone through regulatory clarification)
Data transportability of safety data of gene edited products (in particular, food)

Ministries ask for notification of genome editing, which is on a semi voluntary basis. Overall, this is a transparent policy, particular if you compare it with, for example, Argentina, which has no disclosures at all, or Brazil, which only publishes a summary of the notification (about 1 page on information). The Japanese notifications are more complete, with 5-10 pages of information, and they are also published by the international Biosafety Clearinghouse.

The data transportability is more important. Results could be shared with other governments, particular on the safety assessments that have been done. For example, there is no information from Argentina of what was already assessed, and that is a pity. Data transportability helps to prevent a waste of resources for governments.

Transparency and data transportability are there for GMO, this issue is very important.

How do you look at the future, and is investing in biotech an opportunity to be ahead of other countries? In other technological fields, Japan is much ahead of other parts of the world, for example with electronics, mobile devices, artificial intelligence, etc.

With regards to Artificial intelligence, China is far more progressive.
In Japan, there is a long tradition to produce plastic and other materials, also biorefinery and white biotechnology are large sectors. Synthetic biology would be interesting in this regard, as it may help to create alternative materials. There are four or five districts where the Japanese government is funding innovation in biotechnology as part of its regional economic development program striving towards a "green future" and "bioeconomy". However, the public funding is getting lower and lower over time, and is now not comparable to programs from other parts of the world, such as the US or the HORIZON 2020 program. Universities are semi privatized, and competitive funding is needed.

In addition: the situation in the Netherlands and the EU is discussed, including the view towards genome editing, and the anticipated steps and developments in the regulations of genome editing.

Annex 1.5 Report interview USA (FDA)

Date: 10/11/2021
Organisation of the three interviewees: U.S. Food and Drug Administration (FDA)
Interviewers: [redacted] and [redacted]

Additional comments from interviewers are given in *black italic*; answers are given in blue.
NB: This interview was with three employees from the FDA. This interview is about food derived from plants, one of the work fields of FDA (whereby "food" is defined as "food for man and other animals under the Federal Food, Drug and Cosmetic Act -, so when we say food, we mean food for humans and animals unless we specify otherwise). Environmental aspects of GE plants are not covered by the FDA; other US agencies have authority over environmental aspects of some GE plants.

General / Introduction

- What is the current legal framework for genome edited organisms, particularly for food and feed purposes? Which distinctions, if any, are made between genome-edited animals, plants, and microorganisms?

The Center for Food Safety and Applied Nutrition and Division of Animal Feeds within Center for Veterinary Medicine (CVM) mainly deals with plants, and to some extend micro-organisms. This discussion refers only to human and animal food derived from plants. Animals are not their work field; it is under another authority (Office of New Animal
It is important to understand the background of the regulatory situation. The USA government decided how it was going regulate the products of biotechnology in the 1980's. Currently, products of biotechnology are regulated under existing laws. Food and feed from plants, irrespective of the way they are made, are regulated as food.

Some of the first genetically engineered (GE) foods that were made, were from genetically modified plants. (There were some enzymes – a chymosyin expressed in E. coli k12- developed before the development of GE plants) The properties of the food (from these plants) were very carefully checked for potential safety issues; the focus was on the objective characteristics of the food and not necessarily the process used to develop the plant. Manufacturing process may have an effect, but it is the product and its characteristics that is judged. FDA established a voluntary consultation process, to enable the producers and developers to develop the right information, that enables them to ensure the food they produce is safe and legal.

In 1992 a new policy was adopted, about the safety of all foods derived from new plant varieties. The policy statement explains that food from new plant varieties are regulated under the existing law- the Federal Food, Drug and Cosmetic Act.
Food from a genetically engineered plant, unless they contain an unapproved food additive, does not need regulatory approval. Nevertheless, developers are encouraged to start a consultation process early in the developing process, so the FDA can discuss with the developer potential safety issues that might arise with the food (all of the intended uses in food including by-products). Simultaneously, the FDA is informed about new developments. Once the firm has completed its safety assessment of a product they intend to market, the firm submits a summary of its safety and regulatory assessment to FDA and FDA evaluates the data and information to determine whether there are any unresolved questions about the safety and regulatory status of food from the plant. Once FDA has determined that there are no unresolved safety or regulatory questions the agency considers the consultation to be complete.

With respect genome editing: FDA is developing draft guidance for plants to help developers in the process of ensuring food safety. This guidance will be completed and made public soon.
Food from genome edited plants do not require premarket approval, unless they are or contain an unapproved food or color additive. Importantly, these foods would still be regulated by FDA under its post-market authority. So at no time would such foods be unregulated. They would always have to meet the safety standards of the Federal Food, Drug and Cosmetic Act.

The developer must ensure the food is safe and legal (which is true for any food product)

There is one example of a completed consultation on a food product from a genome edited plant, namely that on the Calyxt soybean oil with increased oleic acid levels. This consultation is publicly available via the FDA website.

Is the oil from this soybean going to be labelled?
Yes, the oil will be labelled to reflect the difference in the composition of the oil, as is done also for any other high-oleic-acid soybean variety. Meal derived from this Calyxt soybean is not compositional different from meal from other types of soybean; therefore, there is no necessity to label it to reflect a change in composition.

Labeling of foods for humans with respect to the requirements of the Bioengineered (BE) Food Disclosure Standard falls under the authority of USDA's Agricultural Marketing Service. Whether human food products from the Calyxt soybean are required to bear a BE label would depend on the nature of the product being marketed and the specific criteria in the BE Food Disclosure Standard.

- What are the main strenghts of the legal framework, and what opportunities does it give?

Policy developed way back 1992? Is that a strength?
One of the great values of the legal framework is that it enables developers and FDA to identify food products that are more likely to have a safety concern – rather than focus on the method or technology that was used to develop the new plant variety. In the end, the safety is the aim of a public health agency. There is value in the fact that food products with identical characteristics are treated the same, regardless of the methods used to create them. Experience also allows to change, offering flexibility to address issues. Hence there is no mandatory approach based on how a product was produced. This flexibility allows the agency to deal with issues such as import of products from third countries.

- What are the main weaknesses of the legal framework, and what threats do you see?

This question is difficult to answer. There are not many genome edited plants yet, and hence there is little experience. Because there is no mandatory pre-market approval unless there is a food additive, there is flexibility to address different types of genetically engineered food products while maintaining the safe safety standard irrespective of the method or technique that was used to develop a food. Allows to assess the safety for consumers in a way suited to the product while also enforcing the relevant law.
Imported products, in general, can be difficult.

Definitions and scope of the pertinent regulations

- What is the definition used in legislation, if any? Is the definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

Q: Genome editing: in guidance: what do you consider as genome editing? What kind of definition is used?
Currently, we are still working on the draft guidance. There are different views internationally on what genome editing entails, and that has to be contemplated. Historically in the USA, there is not so much focus on the process; the focus is on the final product. That is also the case for genome editing.
Historically, FDA has not said "these techniques are in, these are out." The focus is on the food and the characteristics of the food.
In addition, historically, there is also not a focus on the DNA and the type of change(s) made there as a determining factor in regulation. A minor change on the DNA, may have no effect, or may have a (large) effect on food composition. With genetic engineering: you can introduce a transgenic protein, that may not have any effect, or it may have a large effect on the characteristics of the food. It is not so much on the change in the DNA, but the impact on the final product that is important. It is a risk focussed approach. Nevertheless, the information on what happens on DNA level is shared with the FDA in the consultation process. Producers clarify the molecular characteristics which insertions and deletions are present in the plant, include the site and the changes outside the side of insertion. Information on the molecular characterization of the genetic changes in the genome may provide information on the types of changes that might occur in compositional analysis of food.

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?

Q: Early consultations: might provide insight in developments: are there any developments that are of particular interest at the moment?
With consultations starting very early during product development, potential safety issues are identified very early on. This allows also for a case-by-case approach, and allows the developer the decision to continue with product development or not. This also enables FDA to have early discussions within the own organisation on the right approach for a new type of product, and to see what to do, fostering preparedness.

The advice is given on a case-by-case basis, so the developer is guided in what is needed to ensure the safety of a product. The developer is advised what should be investigated, i.e., what the actual questions are, so they can have the right focus. This is appreciated, particularly by smaller developers.
Guidance also can support innovation, so that developers do not waste money on tests and experiments that are not relevant. In addition, when they decided an analysis is indeed needed, the FDA can give advice on the setup and execution (sufficient number of samples, replication, etc) of the experiments, so that the outcomes are meaningful.

With regards to genome editing, early consultations could be helpful with crops that we do not see very often. A tree would be very different than corn for example. With early consultations regulators and developers can help each other to give / search for information, in order to ensure safety of the end product.

Policy makers from other US agencies are also welcome to interact and share their experiences with FDA.

Food and environmental safety
- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" genetically engineered organisms and from conventionally obtained organisms (for example via mutagenesis breeding)?

It is the product that determines the risk, not the technique (See above)

- What risk assessments are carried out? Does it cover food and environmental safety?

The interview only is on food (and feed) safety from plants. Environmental safety is under a different organisation's oversight.

- Unintended effects: how are these taken into account in risk assessment?

See above.

Enforcement, detectability, and traceability
- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from internal market, as well as imported products)?

In case of the only example of genome-edited, high-oleic soybean, the oil had to be labelled for the altered compositional characteristics (not the technology), same as for other high-oleic varieties. See the above comment about BE labelling enforced by USDA's Agricultural Marketing Service.

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of regulations pertinent to products from genetically engineered/gene-edited organisms?

Not addressed specifically.

(Economic) position& Influence on innovation
- What relationship, if any, does the regulatory framework have with innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to worldwide)

The approach of the FDA is to be open, and involved very early in the process. The aim is to provide the best thoughts on new products.
This approach is considered to be positive for innovation (see above as well).

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country?

How is the perception of agricultural biotech.; and the general awareness?
A tough question, in particular because there is not one answer. There are very diverse views in the USA. In general, biotech crops and food products make up an important part of the regular food supply, and therefore routinely consumed as part of the diet of most American consumers. There are groups of consumers that prefer organic products. Some consumers are opposed to agricultural biotech, but there is also interest and excitement about the use of biotech for food production among some consumers. For example, consumers see possibilities for agricultural biotech to bring solutions for sustainability issues.
In addition, there are consumers that are interested in products with new characteristics, such as a better nutritional value. An example is the oil with a more favourable fatty acid composition; a product that has been evaluated several times.

Q:In the oleic oil from genome edited soybean, was it an important question what oil it would replace?
The FDA considered human food, and indeed what oils would be replaced with the new oil with increased oleic acid concentration (acclaimed to be healthier).
In the consultation meetings, developers are stimulated to consider those kind of questions as: "what is the intended use?", to start early in the development about the question where oil may end up.

- Is there a different feeling towards genome editing and other new genetic engineering techniques?

Not specifically addressed

- What is likely the cause of this general view/or different views?

Not specifically addressed.

- How is public perception towards their regulation?

In general, consumers do have trust in the institutions, in particular food safety institutions.

Consumers may not have information, or may not have correct information, about genetically engineered food but also on biotech food. Currently there is a large, multi year effort, ordered and funded by the congress, called "feed your mind". That is to provide correct information and to help people understand.

Links provided on this initiative:
https://www.fda.gov/food/cfsan-constituent-updates/fda-launches-feed-your-mind-help-consumers-better-understand-science-behind-foods-derived-genetic
https://www.fda.gov/food/consumers/agricultural-biotechnology

International harmonization:

- What aspects should be harmonized internationally in your opinion?

See below

- Does your government strive towards international harmonization?

Yes, for risk assessment. Where applicable or possible, the government strives towards harmonisation.

Although the experience here is that it is very valuable to have some practical experience with assessing / evaluation the food safety of new products. In discussions some know-how from practice is really valuable, not only theoretical consideration.
For genome edited products, so far only 1 product has been evaluated.
In terms of harmonization: having experience with products is key, before you try to harmonize.

As Final statement: It is the product that finally has to be good and safe. It is not that the process may not have any effect and cannot have an influence, but it is the product that counts in the end. The phrase "Product, NOT the process" is often quoted, yet information on the process can still contribute useful data to the risk assessment, which may vary from one product to another in the nature of questions being posed.

Annex 1.6 Interview Canada (HC)

Date: 18/11/2021
Organisation of the interviewee: Health Canada (HC)
Interviewers: [redacted] and [redacted]

Additional comments from interviewers are given in *black italic*; answers are given in blue.

General / Introduction

- What is the current legal framework for genome edited organisms, particularly for food and feed purposes?

The Canadian legal context for genome edited organisms is complex, as several governmental organisations are involved.
When regulations for genetically modified (GM) organisms in general were made, a product-based approach was taken. Following the current regulations, genome edited organisms fall within the regulatory framework for novel foods (which can include foods derived from GM organisms). The criterion for a GM organism is whether there has been an intentional change in heritable traits of an organism; on that basis, any breeding technology resulting in an intentional change in a heritable trait is considered genetic modification, and the products from these techniques might be novel foods. However, to avoid all new food products being captured and assessed, food from a GM organism is only a novel food if the GM organism gains a new characteristic, loses an existing characteristic, or has an existing characteristic changed such that it falls outside the known range for that organism. This is described in Division 28 of the Canadian Food and Drug Regulations.
There are several government agencies which may assess products developed using genome editing. The environmental assessment for plants is the purview of the Canadian Food Inspection Agency (CFIA). The environmental assessment of animals and micro-organisms are under the purview of Environmental and Climate Change Canada (under the Canadian Environmental Protection Act).
The food safety assessment of novel foods (including foods derived from GM and genome edited organisms; whereby it has to be under the Canadian Food and Drug Regulations, there is no distinction between what is considered to be traditional GM (i.e., rDNA-based organisms) and genome-edited organisms) foods falls under Health Canada's oversight.
Livestock feed safety is assessed by the CFIA.

- Do plants, microorganisms and animals all fall within the same framework? If not, what distinctions are made between them?

Regarding the novel foods regulatory framework, no distinctions made in the 'novel food' definition between products from animals, plants or microorganisms. Also, no distinctions are made between the processes used to develop a product.
(Different agencies involved in the regulation, see above).

- What are the main strenghts of the legal framework, and what opportunities does it give?

Decisions are made on the characteristics of the products, i.e. whether it is a novel food, which affords flexibility.
In practice, the products assessed are those with new (additional) characteristics. To date, few novel foods have been products based on removal of qualities or characteristics.
Products derived from GM organisms can be considered novel and undergo pre-market assessment, however if the genetic modifications only result in a product with characteristics comparable to what is already on the market, than no pre-market assessment is needed (i.e., the product is considered not novel).
A strength is that there is no list of approved techniques or a list of regulated techniques. If there is a new technique developed, there is no separate decision needed to see if a technique has to be added to a list of regulated or exempted techniques. In that sense, the legal framework is future proof.

- What are the main weaknesses of the legal framework, and what threats do you see?

There is a fair amount of grey area (i.e., vagueness) in the definition of a novel food. For example, what is considered a new or altered characteristic? If you see 1% variance in an existing characteristic, is it then considered novel? Such variance can also originate from environmental conditions, for instance the soil in the location where a plant grows.

The consultation process involved takes time, both for the developers, that need a significant amount of time to generate the required data for the safety assessment, and the assessment from Health Canada takes approximately 410 days to complete. Another challenge is that, based on the definition of a novel food, sometimes a precedent is set. For example for a certain herbicide tolerance characteristic: if this was assessed in the past, the expectation is that it has to be assessed again. If you see the same herbicide-resistant trait multiple – like 15 – times, under the current legislation, it is always a novel characteristic. There is no clear moment to declare when a specific characteristic is no longer novel.
There is no specific legislation for biotechnology by the Government of Canada. There are slightly different definitions used for novel items in the different legal acts. Regulatory steps are different for the approval of novel food products (depending on their origin), novel feed products, and for the environmental release of plants with novel traits (PNTs). There are potentially three (typically two) governmental agencies involved, and therefore it can be difficult for developers to navigate through the Canadian regulatory framework.

Definitions and scope of the pertinent regulations

- What is the definition used in legislation, if any? Is the definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

(See above for GM)

Definition of novelty: in the EU this is defined as substantive use in the EU before 1997 (when novel food legislation was adopted). For products with traditional use outside EU there is a fast track procedure.
The Novel Food Regulations are not specific to foods derived from GM organisms, they also include foods with no history of safe use and foods treated with a novel process which causes a major change (defined in the regulations) to the treated food. In Canada, products that were already consumed before 1999 (when legislation was created) are not novel. Regarding the history of safe use of a food, it does not matter where the safe use was. If you can demonstrate that the food has a history of safe use anywhere, it is acceptable. However, like the aspects of the novel food definition which deal with GM, we also face challenges regarding the interpretation of what is a sufficient history of safe use: how much data do you need, how long must the history of use be. Here, it could be good to have a more black and white situation.

Gk: Imagine a mutation introduced by genome editing: is it a valid argument if this mutation could have been created by a conventional method (to not be considered novel)?
In our current approach: if it could have been by conventional method, it means the product can still be novel. Thus for a genome edited product, the fact that it could be theoretically developed using conventional methods, this is not a valid argument for why a product should not be novel (i.e., require pre-market assessment).
If there is a product with the exact same mutation, and a developer can demonstrate that it exactly the same, you can discuss if there is a necessity for an assessment. In practice, this argument has not been used often and so far this rationale has only been applicable for a company to prove the similarity between their own products.

Nevertheless, we recently held a consultation on new guidance pertaining to products of plant breeding including those developed using genome editing (this is only for plant breeding and plant products, thus not for animal or micro-organisms). We are creating new guidance on what is a novel food derived from a product of plant breeding and what is not. Herein, the scope of what is a novel food is narrowed, with five criteria to be considered.

Regardless of the method used the following foods are not considered novel:

1. Foods derived from plants with genetic modifications that do not alter an endogenous protein in a way that introduces or increases similarity with a known allergen or toxin relevant to human health;

2. Foods derived from plants with genetic modifications that do not increase levels of a known endogenous allergen, a known endogenous toxin, or a known endogenous anti-nutrient beyond the documented ranges observed for these analytes in the plant species;
3. Foods derived from plants with genetic modifications that do not have an impact on key nutritional composition and/or metabolism;
4. Foods derived from plants with genetic modifications that do not intentionally change the food use of the plant; and
5. Foods derived from plants with genetic modifications that do not result in the presence of foreign DNA in the final plant product.
   -Regarding impacts on key nutrients (i.e., Key nutrients are considered any nutrients listed in the Dietary Reference Intakes (DRI) that have a nutrient-based reference value associated with adequacy (i.e., an Estimated Average Requirement [EAR] and Recommended Dietary Allowance [RDA] value or an Adequate Intake [AI] value) and/or those with established adverse health effects (i.e., a Tolerable Upper Intake Level [UL] value). All four reference values are directly associated with consumer health

   The public consultation on the new guidance received approximately 4700 comments.
   Our expectations with the new guidance are that 99.9% of conventionally bred products of plant breeding will not need require pre-market assessment (i.e., are novel). For genome-edited plants it depends on the introduced characteristic(s) (see the above 5 criteria), but rDNA-derived products still have to be seen.

There is a second piece of guidance for novel foods derived from plants which are considered 'Retransformants'. This pertains to novel foods derived from plant products that are comparable to plant products that have already been previously assessed as novel foods. If you introduce an identical cassette of foreign DNA to what you have already used before (retransformation) there is still the obligation to notify the authorities for pre-market assessment. However, less information is required for the assessment of retransformants, and the assessment will be quicker (estimation in 120 days, instead of 410 days). A thorough molecular characterization is still required as it will help establish whether there is substantial equivalence to a previously assessed plant product. If the molecular characterization shows that the new product is not comparable to the previously assessed product (i.e., it is not a retransformant), then a full pre-market safety assessment will be required. In this regard, the guidance is agnostic to the method used (be it rDNA or gene editing).
The retransformant guidance will be applicable to products such as potatoes with 15 different lines with the same transgenic construct. It could, for example, also be relevant for sugar cane varieties with the Bt gene, now being developed in Brazil: Multiple products with the same cassette.

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?

For synthetic biology: we have the impression we are fairly well prepared.
For cellular agriculture: this has posed some questions, as to what extent such products would be considered novel foods.

Overall, the trend we see in biotechnology is one towards even greater precision, whereby developers can characterize products better, with increased understanding of the changes in their products.
There would only be a real challenge if a new technology would be like a 'black box': when developers cannot explain what is changed in their product (which is against the trend).

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" genetically engineered organisms and from conventionally obtained organisms (for example via mutagenesis breeding)?

Recently, a review paper was published on this (Schnell et al., 2015), about the unintended effects of DNA insertions. The main message on unintended effects is that they do exist; yet they also exist in conventional breeding. Science shows unintended effects are not specific or unique to new techniques of modification.
There is no reason to base regulatory oversight solely on the potential for unintended effects.
There can be unexpected (unintended) effects at the intended location in the genome, or of the protein you

change. Based on the current guidelines, a thorough molecular characterization is done. This characterization will give the information needed, either that are no significant unintended changes, or if further information is required to demonstrate product safety.

Do insertions introduced during the breeding process, but segregated out in further breeding steps, need to be assessed?
No, it is the final product that counts. Any unintended or intended introduction of genetic material in the breeding process does not matter, as long as it is segregated out and not present in the final product. Because there will be no exposure to these materials, there is no risk to these materials.

Under Novel Foods, we also consider new processing technologies, to see if a processing technology that is applied for the first time to a food, causes that food to undergo a major change (defined in the regulations). So far, not a lot of foods treated with novel processes have been assessed: Ohmic heating is a different way of heating food for example, but it is still heating. An example of a novel food resulting from a novel process is high pressure processing(HPP)-treated foods: After approximately 15 assessments of these types of foods, HPP-treated foods as a whole are seen as safe.

- What risk assessments are carried out? Does it cover food and environmental safety?

See above.

- Unintended effects: how are these taken into account in risk assessment?

See above.

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from internal market, as well as imported products)?

No specific requirements for GM food labelling, and we do not ask for a detection method.
The Standards Council of Canada officially adopted the standard for Voluntary labelling and advertising of foods that are and are not products of genetic engineering in 2004 (standard reaffirmed in 2021).
Mandatory labelling for all foods, including GM foods can be required for health and safety purposes (e.g., when an additional allergen is present or when the composition of a food is significantly changed). In case of the high oleic soybean: its oil has to be labelled as "high oleic soy bean oil", not just "soy bean oil".

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of regulations pertinent to products from genetically engineered/gene-edited organisms?

The enforcement of the Food and Drugs Act is by the CFIA.

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to worldwide)

How is that in Canada, in particular in light of the four agencies involved?
The main aim of the regulation is ensuring that products can be put on the market safely. It is not there to unduly impede the market introduction of products that are safe.
However, in doing the assessments, it is the safety that determines how the assessment is done, other aspects, such as economic impact, are not taken into account.

In conversations between the different organisations involved in novel food products, it is a factor that the rules and assessments should not be overly burdensome. The main driver is what you want to look into for safety reasons.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country?

How is the perception of agricultural biotech.; and the general awareness?
There is some work done on general public sentiment towards biotech in Canada (although the interviewees address this is not their main focus)
There is a percentage of consumers (around 20% approximately) that are opposed and strongly opposed, and about 15% of the consumers are in favour of the use of biotech for agriculture. The rest, the majority, is in between (mixed or agnostic).
When posed the question: do you think GM foods should be labelled? The vast majority will say that it should be. Only a few percent of the consumers would say no or do not mind a lack of labelling.

When the general public is asked what their food safety concerns are in general, GM does not come to mind. According to the interviewees, the perspective of the employees at Health Canada on consumer acceptation may be a bit biased on this point, as the consumers we hear from are those that are strongly opposed to GM. Regulators most often hear from people complaining, which creates a skewed impression.

- Is there a different feeling towards genome editing and other new genetic engineering techniques?

Not a great difference in feeling. The majority of the public considers genome editing and other new techniques as genetic modification.

- What is likely the cause of this general view/or different views?

Not relevant

- How is public perception towards their regulation?

Not specifically addressed.

International harmonization:

- What aspects should be harmonized internationally in your opinion?

Canada is definitely in favour of harmonization.
Canada participates in international initiatives (such as OECD and Codex), and it is also constantly following the developments of major trading partners.
Unless there are considerations really specific to Canada, we want to have the regulations aligned internationally as much as possible. This is also the purpose of OECD and Codex. Harmonisation is mainly useful for trade purposes, but it is also logical since everyone is studying the same science as a basis for the legislation.

Currently there is a project with FSANZ, exploring how we can use each other's pre-market safety assessments for GM foods to support our own regulatory decisions regarding these products.

- Does your government strive towards international harmonization?

Yes, see above.

Annex 1.7 Interview South Africa

Report interview with Biosafety South Africa on 7 December 2021

Date: 7/12/2021
Organisation of the interviewee: Biosafety South Africa
Interviewers: [redacted] and [redacted]

Questions for interview with Biosafety South Africa, 7 December 2021

Background on Biosafety South Africa

Biosafety South Africa is a service platform. The initial focus of the institute was merely on safety, but now it has a more broad view and approach, with a central place for sustainability. Its remit is broader than just GMOs and has evolved to cover, for example, laboratory biosafety, sustainability, and innovation, but also viability and social aspects besides safety.

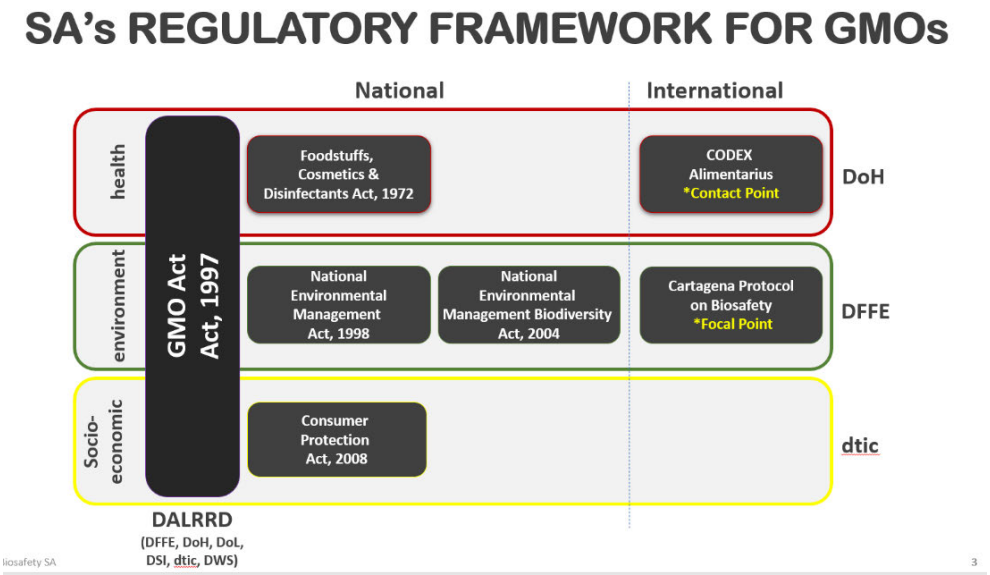
It is a government funded platform, to help developers to support innovation, in a sustainable way.

General / Introduction

- What is the current legal framework for genome-edited organisms in South Africa, particularly for food and/or feed purposes?

In South Africa, we have the GMOs Act since 1997; that primary regulates GMO. The infrastructure for decisions on GMOs include an Executive Council, with members from seven different government agencies. They make the decision if a GMO is allowed, and they work on a basis of consensus (no voting principle). There is a Scientific Advisory Committee: gives advice from a scientific point of view to the Executive Council. This is comparable to the EU, with both scientists and bureaucrats having a role in decision making.

GMO Act cuts across several domains, the Department of health covers the health and food safety related aspects. The environmental aspects are under the Department of forestry, fisheries and the environment. Besides the socioeconomic parts are for the Department of Trade Industry and competition, and the Consumer Protection Act from 2008 covers labelling aspects for GM organisms (besides, for example, those for nutritional aspects), which still has to be finalized.



The term New breeding technologies (NBTs) is preferred. Currently, all NBTs fall under the GMOs Act in South Africa. As long as Genome editing is considered GMO, it should be labelled under the Consumer Protection Act.

By the end of October 2021, the Executive Council decided to regulate new breeding technologies (NBTs) as GMOs. The background of that decision was that, since 2017, there had been internal discussions on the regulatory framework, and whether it should be changed to accommodate NBTs. In 2017, the Executive Council asked recommendations from the Scientific Committee on NBTs. There were several iterations before a decision was made (because consensus needed). The recommendation the Executive Council received was based on the interpretation of the legal definition of GMO in the GMO act, which had been done by scientists. Thus, the policy advice is based on the legal interpretation by scientists and bureaucrats. The Executive Council wanted to get this through without considering amendments to GMO Act.
Biosafety South Africa also requested a formal legal interpretation (has been published): and that interpretation said that the GMOs Act is ambiguous, you can read process or product based. Yet the Executive Council decision is solely process-based. In general, a process-based approach is more preferred with a more precautionary approach but it will widen the scope.
There is now a formal appeal against the decision. A clear definition is needed plus oversight like that in Argentina.
Biosafety South Africa maintains the view that risk assessment is only a component of the risk analysis framework, which is a robust internationally harmonized process.

- Do plants, microorganisms and animals all fall within the same framework? If not, what distinctions are made between them?

Not addressed specifically.

- What are the main strengths of this legal framework, and what opportunities does it give?

Not addressed specifically.

- What are the main weaknesses of the legal framework, and what challenges do you see?

There is a lack of confidence by the regulators in Africa, despite 30 years of experience with GMOs.
Regulatory frameworks were made after GMOs became controversial.
In the early 2000s, several GMOs with single traits were approved. When the first stacked events arrived, regulators ground to a halt for more than 2 years, because in the absence of specific regulatory provisions, they had to decide how to deal with these stacked events.
Now something similar has happened for genome editing. In 2017, there was an advice, and it took the government until 2021 to come with a statement of one page.
Some regulators have a high-level of reluctance towards new technologies, while we need confidence in and support for innovation.
So far, only the anti GMO lobby has gone to court on GMO-related matters. Regulators are more conservative towards a decision so that they can avoid court cases, because strong opposers are most likely to go to court, while companies will tread lightly. Regulators tend to lean towards the ones they are afraid of.

Definitions and scope of the regulation

- What is the definition used in legislation for the product category/-ies which encompass(es) genome-edited products? Is this definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

South Africa has a definition for genetic modification that is very similar to the European definition, also based on export-related arguments. The latter also applies to other fields, such as requirements for grapevines. Hence one should be cautious with extrapolating from GMOs to other fields.
The Cartagena definition was not there yet when South Africa adopted GMO legislation.
Regulators tend to look towards Europe as a leader for examples.

Genetically Modified Organisms Act (SA): "GMO means an organism the genes or genetic material of which has been modified in a way that does not occur naturally through mating or natural recombination or both".
The current process-based interpretation focusses on " has been modified in a way".
A more product-based would take "organism the genes or genetic material of which" as reference point.

(Extra comment on definitions:
Many different terms such as genome editing, genetic engineering and genetic modifications. What term you use can have large implications in the regulatory environment.
I advocate the use "induced genetic variation (can cover GMO, and for example SDN-1, but also mutagenesis)".

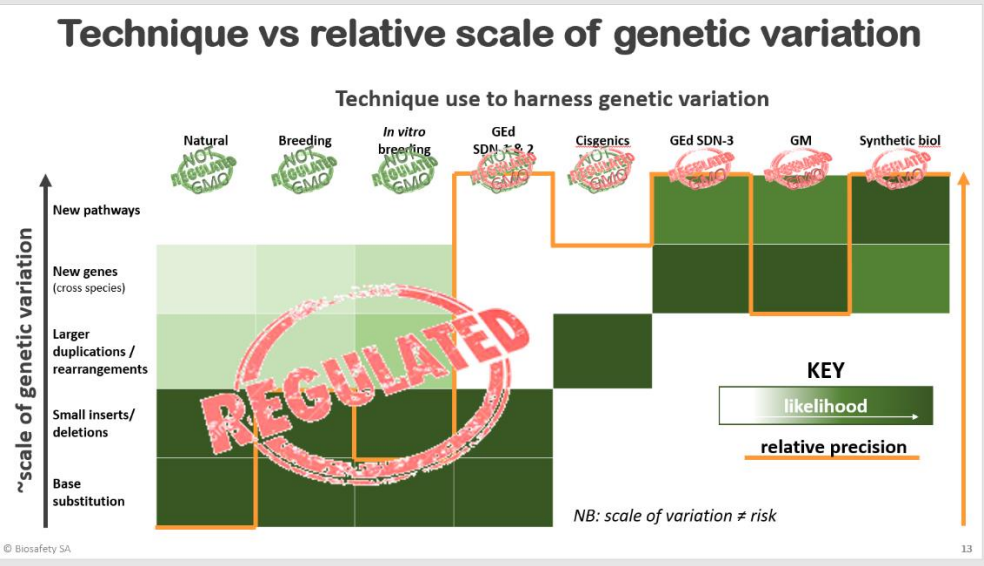
- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?

Not addressed specifically.

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" genetically engineered organisms ad from conventionally obtained organisms (for example, via mutagenesis breeding)?

In other parts of the world, a science-based, fit-for-purpose risk analysis is employed, on a case-by-case basis. This can handle NBTs, gene drives and synthetic biology. Also benefits should be considered besides risks. The techniques have to be offset against the scale of genetic variation in nature, which is considered to represent no risk.
In the discussion on off-target effects: genome editing technologies, such as CRISPR-Cas are much more precise to what happens in nature. We want to regulate something that is less likely to induce risks, than natural occurring processes.



Thereby I have to mention that scale of genetic change is not equal to risk.
In addition, in conventional breeding process is there still a risk, for example there is a case where conventional breeding practice led to more allergens in a maize.
NBTs have a smaller or equal risk to what occurs naturally, therefor it would be good if they were regulated conventionally. Thereby it has to be stressed that there are no unregulated products, as other legislation still covers them. For food crops, new varieties are regulated everywhere in the world; thus also in South Africa.
When an organism or product is over the threshold, for example it contains foreign DNA, it should be regulated under a GMO law. GMO legislation, should be for what it was intended for.
In my opinion the Cartagena protocol has a better principle than SA law at the moment, because in Cartagena there is the concept of " novel combination of DNA". In that respect, SDN1&2 are not different from other mutations not regulated as GM. The risk (rather than the process) should therefore be regulated.
The governance proposed is based on that of Argentina (which has aligned its legal definition with that in the Cartagena Protocol), which would entail a change in definition, for example.

- What risk assessments are carried out? Does it cover food and environmental safety?

Not specifically addressed.

- Unintended effects: how are these taken into account during the risk assessment?

Not specifically addressed.

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from the internal market, as well as imported products)?

The rules in the South Africa are broadly the same as those in the EU. You can only use a GMO when you have a permit. A condition to have a permit, is that you should have a detection method in place for the GMO (also needed for the Cartagena Protocol).

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of novel products/genetic engineering/genome editing regulations?

For a point mutation you could design a method, for example a specific PCR.
But when you are considering international trade it is more problematic. For example in the USA, all SDN-1 and SDN-2 organisms are not regulated, and reporting is based on are voluntary systems. Similarly in Australia, SDN-1 is not regulated. There will not be a list or a database with all genome edited products, thus how can it be checked by the government? These checks will fail to recognize certain genome edited products.
How the implementation of the regulation in South-Africa will work, remains an open question.

Labelling requirements have changed over time. This had industry deciding over how to label products with, for example, inconsistent wording.

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with your country's innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to other countries worldwide)

Innovation is considered very important in South-African context, as it is very important for development and local sustainability (though not at any cost), as evident from the mention of innovation in the new name of the Department of Science and Innovation. Innovation can lead to job creation, and economic opportunities, in a sustainable way.
For innovation to work out and to be viable, there should be a market for its products. Thus perception of technologies and products is very important

In my opinion, the only scientifically justified approach, is a product based approach, process does not make sense. A process can be used to create a product with only a very small change, but also to have a very large modification. And vice versa, the same product can be obtained with different technologies.
However, we should not ignore all non-science parts. Perceptions are important, and if you do not have acceptance in the market, you do not have product.
Risk assessment should always scientific, but the communication may have to go beyond that. There should be freedom for consumers to make a decision, on scientific grounds but also on other grounds.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country? What difference is there in the perception of agricultural biotechnology as compared to other forms of biotechnology?
- Is there a different feeling towards genome editing and other new genetic engineering techniques?
- What is likely the cause of this general view/or different views?
- How is public perception towards the regulation?

Currently, Biosafety South Africa is doing a lot of communication work. We look, in collaboration with social scientists, at perception of biotechnology and do socioeconomic research. (This in the context of the National

Biotechnology Strategy from 2001, and the National Bio-economy Strategy from 2014).
The great majority of South Africans (94%) does not know what you talk about when discussing biotechnology. In addition, a large number does not care, there are many other concerns on their mind, how natural things are is not a main concern.
The population can be seen as a big oval lemon, with the majority not having an interest, but there are a few people with extreme views at both ends. These consumers with extreme views have all the discussion, but this represents only about 2% of the population.
Currently, we have an affluent market; and retailers are just managing the situation.
Very small group of opiniated people can have a large impact, for example on decisions of retailers to sell certain products. Retailers may want to prevent protest outside their stores.

For the first generation of GMOs, the advantages were clearly aimed at farmers and the benefits they could have from these GMO crops.
Currently, the market has an almost maximal saturation for GMOs. All cotton that is cultivated in South Africa is GM (Bt), and I expect about 98% for soy and 85-90% for maize. For the last one there is a GMO free market. What crop species farmers will decide to grow is season-dependent.

Has COVID has had any impact on the public opinion of GMOs (as some of the vaccines are made from GMOs)?.
There has been no such impact. I may be a bit naive/optimistic in the issue of public opinion and perception; to illustrate, there is far more opposition towards obligatory vaccination than I had anticipated on beforehand. This is a political issues, where no risks are taken and force is avoided.

International harmonization:
- What aspects should be harmonized internationally in your opinion?

Not addressed specifically.

- Does your government strive towards international harmonization?

Not addressed specifically.

I consider the Cartagena protocol under the Conventional on Biological Diversity appropriate for synthetic biology applications. They can be adequately assessed with risk analysis tools that we have now as for any GMO. These should accommodate uncertainties and variability.
The Cartagena protocol is a broad framework, that has the principles for risk analysis, and should be seen as an intellectual guide. For each particular case it should be decided how to apply, the protocol should not necessarily be followed exactly.
In general it is a good framework, based on international best practices. I agree with broad framework – as long as not all nitty gritty details should be prescribed.
Within Africa, there is a lack of public confidence in regulators and also little experience. Governance has only been established because of turmoil.
In the 19 countries that have or have adopted regulation for NBTs: 16 introduced oversight similar to the American USDA's "Am I regulated" procedure.

Annex 1.8 Report Interview Canada (CFIA)

Date: 07/12/2021
Organisation of the interviewee: The Canadian Food Inspection Agency (CFIA)
Interviewers: [redacted] and [redacted]

General / Introduction

- What is the current legal framework for genome-edited organisms, particularly for food and/or feed purposes?

Legal framework and role of CFIA:
Canada has a biotech framework, consisting of different acts, *e.g.,* the Canadian Environmental Protection Act (also referred as CEPA) (anything new and different will be of interest); Seeds Act and Regulations; and the Feeds Act and Regulations.
In Canada, the regulation of biotechnology products, depending on their intended use, falls under the mandate of the Canadian Food Inspection Agency (CFIA), Health Canada (HC) and Environment Canada (EC). CFIA provides all federal inspection services related to food and enforces the food safety and nutritional quality standards established by HC.
The CFIA is also responsible under the Seeds Act and Seeds Regulations for regulating the importation, environmental release and variety registration of plants with novel traits.
The manufacture, sale and import of livestock feeds including novel feeds are regulated in Canada under the Feeds Act and Feeds Regulations administered by the CFIA.
Under the authority of the Canadian Environmental Protection Act (CEPA 1999), EC is responsible for administering the New Substances Notification Regulations (Organisms) and for conducting, with Health Canada, environmental and indirect human health risk assessments of 'new' substances including organisms and micro-organisms that may have been derived through biotechnology
Under the Seeds Regulations, regulation is triggered by the potential of a plant to have an environmental impact. The framework is structured so that anything that is neither new or different is captured. Captured are new plant species, but also any plant that can have an impact (weediness, non-target organisms, plant pest, biodiversity, gene flow to related species). The question therefore is how it impacts the environment, not how it was made.

For feeds, the legislations covers sales, manufacture and import, whilst in 1996, the component of biotech was added. This slides under the existing framework. As for other feeds, the same endpoints apply: animal health, human health (food safety), worker bystanders, and the environment. Environmental aspects need not be dealt with by Environment and Climate Canada as this is already covered by CFIA.
In 1996, novel feeds were defined as
1. being derived from an organism that is not included in Schedules IV and V (positive list of ingredients): If it is not listed, it is not allowed, OR
2. bearing a novel trait (includes biotech plants, micro-organisms, animals), which also captures cellular agriculture;
Note: the list of positive ingredients is the comparator: accessible within the regulation.

- Do plants, microorganisms and animals all fall within the same framework? If not, what distinctions are made between them?

For all products, it is the intended use that determines which frameworks will apply. For example, for a plant, this depends on the usage of the plant, *e.g.*, food use? Seed for planting? Likewise, what is the intended use of a microorganism, *e.g.*, for remediation refer to Environment, and for use as a fertilizer to the Fertilizer Program, etc. Animals are handled in the same way as plants when it comes to food and feed uses. However, the environmental release considerations fall under the responsibility of Environment and Climate Change Canada (ECCC) (using CEPA). ECCC may rely on other federal departments to support their decision-making such as the department of Fisheries and Ocean (DFO) for fish. For example, in the past, ECCC involved the

Department of Fisheries and Oceans if the animal is a fish. CFIA maintains good relationships with the other agencies to track and share information on products under review.

- What are the main strengths of this legal framework, and what opportunities does it give?

Reason for framework: Intricacy, with feed experts assessing feeds, etc. instead of a specialized group assessing only biotech products. If the feed is equivalent to any other product, then the product is not treated differently.

The environmental release program is flexible and can accommodate new technologies such as gene editing under the same outcome-focused operating principles, so that no update of regulations will be needed when new technologies are developed. There is also lots of flexibility with regard to information requirements. The strength is that we do not describe data requirements specifically in the Regulation, and can instead provide regulatory guidance that is adaptable to new developments. While there are a number of criteria that need to be addressed by the applicant, the guidance is quite flexible with regard to what data and which approach is used to address these criteria.

For feed, the same aspects as previously mentioned trigger a premarket assessment. The same kinds of strengths and weaknesses apply: the framework is flexible, but with new technologies, there are challenges with determining what is novel and what is not novel. The regulations are not prescriptive with regard to data requirements, the proponent has to provide information to satisfy the assessments end-points, i.e., (in terms of animal health, human health via food residues and worker/by-stander exposure, and the environment) and effective for its intended purpose. The evaluation also ensures that the feed is accurately defined in the Feeds Regulations and is labelled appropriately for its safe, effective use and for consumer protection.
An additional strength is the positive feed ingredients found in the Feeds Regulations. If an ingredient is not listed in the Schedules, for example hemp products, these products would require a pre-market assessment. Hence this is not because of the hemp being modified using biotechnology tools, the same principles apply to other ingredients that are not listed in the Schedules.

The Seeds Regulations, paragraph 108(c), takes into account past decision taking, for any product derived from something that is already in the environment or assessed. This allows for conventional breeding of authorized products and stacking traits without triggering new assessments.

Under this policy on retransformations and remutations: This is an expedited review that makes the procedure simple for developers: not the whole data package is needed for a retransformant, along the lines of flexibility offered by this policy. Developers notify CFIA of the new transformation event, and, provided that the same DNA construct was used and the developer observes the same traits, no assessment is performed. The CFIA issues a new authorization letter based on the initial assessment. This is logical since there's no expectation that additional data about the second transformation event (same DNA, same trait, same species) would cause CFIA to reach a different conclusion.

The Arctic apple serves as an example of a retransformant. The first recombinant DNA apple, *cv.* Granny Smith, was assessed and authorized. The applicant then introduced the same DNA construct into a different variety (Fuji). The fuji event did not require premarket assessments under the Feeds Regulations

Waxy corn is a good example of an exemption – it was determined to be "non-novel". In this corn, the activity of an enzyme was suppressed, with an absolute similarity to a longstanding conventional mutation with regard to mechanism and phenotype.

- What are the main weaknesses of the legal framework, and what challenges do you see?

A trade-off of an adaptable and flexible regulatory framework is that it is not a simple system - there are no black-and-white rules. With this, there are still a lot of case-by-case judgment calls to be made, *e.g.,* whether there is an impact. We've heard that developers may be reluctant to consult with the authorities. There may be hesitance to develop something that may require a pre-market assessment, and so developers may choose to avoid pursuing certain innovations in Canada. It used to be a simpler world with only recombinant DNA, but with gene editing, we have to describe more clearly when there is an environmental

impact or what is considered novel under the *Feeds Regulations*. This is challenging when considering the range of possible traits and mechanisms, the range of crop species and wild relatives, and the environmental impacts of various agricultural practices. This is very difficult to write in a concise piece of guidance that is still easy to understand.

Definitions and scope of the regulation

- What is the definition used in legislation for the product category/-ies which encompass(es) genome-edited products? Is this definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

Novelty of a product is the regulatory trigger for the various regulatory frameworks in Canada. With regard to novelty, this is covered by our focus on outcomes. This is flexible: there can be ambiguity, especially in the environment. In Canada, the regulation of biotechnology products, depending on their intended use, falls under the mandate of the Canadian Food Inspection Agency (CFIA), Health Canada (HC) and Environment Canada (EC). It is important for a proponent to consider the intended use of their products in order to determine how it is regulated. Although the definitions for novel products across the different pieces of legislation have similarities, there are differences.

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?

Technologies are covered very well by the flexible approach. Guidance need to be updated to provide greater clearance and predictability to regulated parties. We keep learning. Regulatory guidance remains targeted and focused. For feed, our definitions have covered technologies, and would already have done so in the 80s prior to amending the Feeds regulations in the 90s to capture products of biotechnology. Our definition does capture feed products derived from cellular agriculture. There is a constant evolution in data requirements; however the assessment end-points remain the same. For examples, whole genome sequencing is better tool in providing information on the identity of microorganisms as compared to phenotypic methods. Yet such tools do provide some challenges as data from WGS is challenging microorganism nomenclature and the listing of these ingredients in Schedules IV and V of the Feeds Regulations also need to adapt. The Regulations are outcome base in terms of data requirements written at a high level, you can have a guidance that is always adapting to the technology, while information has to meet the endpoints. Build the story so that when it is submitted, the safety (and efficacy for feeds) can be assessed.

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" genetically engineered organisms and from conventionally obtained organisms (for example, via mutagenesis breeding)?

[not addressed specifically]

- What risk assessments are carried out? Does it cover food, feed, and environmental safety?

[see above]

- Unintended effects: how are these taken into account in risk assessment?

The context is that there is a lot emphasis and responsibility placed on product developers to ensure they are not introducing unsafe products into the market. Under the risk-based approach, the assessment may not necessarily be looking into unintended effects. Developers already do this for product development with a system in place, even before the pre-market assessment. Developers need to be on the look-out for things. Breeding itself is a robust process, *e.g.,* by selecting backcrossing, which should be up to expectation before they present the data to us. Variety registration is the next step: breeders and producers get together to assess the quality of the variety. This is not a governmental discussion but a panel (*i.e.,* a recommending committee, variety register and market place (expectations for quality).

Pre-market assessment is just a piece of a larger system, and there are many filters for unintended effects, for gene editing in particular as a set of new, related techniques. We are scientists and we want to make sure that we keep up with the field. We study scientific literature to understand the potential of off-target effects of the technique, and commission studies to report on these effects. We have been following this very closely. So far no UNIQUE risks have been identified associated with these techniques.

It is the product that triggers a pre-market assessment, and endpoints are the same for feeds, e.g. safety and efficacy. The pre-market assessment follows a conventional risk assessment paradigm, *i.e.* identification and characterization of hazards along with exposure assessment, is the same for every type of product, for some there may be more data needed on characterization (novel items). It is not so much about the risk of the technique.
The same type of approach is followed as for other products. For example for corn: If normal corn is imported from an African Swine Fever area, it is considered a high risk. It depends on the product, *e.g.*, if you raise insects on manure: the risk is high, for example. Codex guidelines are being followed.

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from the internal market, as well as imported products)?

There is a risk-based approach towards enforcement, not to go out and just test. Authorized biotech products are considered to be as safe as conventional products. Should we ever need to detect, then developers should have a method available, although this need not be provided during pre-market assessment. For example, for withdrawal from the market, we need to be able to verify if it is off the market. In the case of GM wheat, an unauthorized wheat was detected on a roadside, hence there was a need to have a detection method and be able to follow the GM Wheat and confirm that there was no GM wheat in our supply chain. This was an isolated case, though. We will detect when there is a need to do so, but not for all GM products.

There are no specific biotech/GE labelling requirements under the Feeds regulations, except for conventional labelling requirements that are applicable to all feeds. With regard to detectability, a method will only be asked for if this required from an efficacy or safety perspective. Usually for efficacy, *e.g.* an enzyme claimed to be phytase on the label, one has to identify the phytase, but not the GM event. The method is used to verify compliance of the product against its' approved label *e g.* 50,000 phytase units.

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of novel products/genetic engineering/genome editing regulations?

[not addressed specifically]

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to worldwide)

Regulators do not make distinctions regarding post-market, not advocating for or against. They recognize that the regulatory system has an impact on innovation. There is a continuous cycle of trying, ensuring that the guidance is clear, asking for the need to know items.

Our role is in providing an efficient and logical regulatory system that enables innovation, not placing undue burdens, whilst being neutral in making decisions which should be based on scientific factors. There is much flexibility especially with regard to gene editing, whilst applicants ask for clarity. We are trying to work on that and provide better guidance. Developers have a responsibility to be aware of if their product requires pre-market assessment or not; we also have our role in there and can provide opinions on regulatory status upon request.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country?

[not addressed specifically]

- Is there a different feeling towards genome editing and other new genetic engineering techniques?

[not addressed specifically]

- What is likely the cause of this general view/or different views?

[not addressed specifically]

- How is public perception towards the regulation?

The debate has become politicized.

As regulator, we do not have a large role in public debate. The responsibility of Agriculture and Agri-Food Canada is to support producers, *e.g.,* farm incomes, marketplaces, investment programs, and can play a role in public attitude monitoring. Our own role, for example is to be able to explain to our regulatory system and our assessment conclusions. Government likes to promote innovation but at an arm's length from the regulator. There is a separation of duties when it comes to socio-economic issues.

International harmonization:

- What aspects should be harmonized internationally in your opinion?

International harmonization is considered important, not from a trigger perspective but in terms of data requirements. Codex guidance and others (e.g., OECD consensus documents) have helped a lot: provide data to support X,Y, and Z. There is a lot of power to it. Industry also has had a chance to provide an input. Codex guidance is used a lot within the division (feed).

- Does your government strive towards international harmonization?

A lot of financial support goes into multilateral forums for that purpose. CFIA works with OECD, *e.g.*, developing consensus documents, such as for molecular characterization, environmental considerations. There are also frequent interactions with, *e.g.*, US FDA, USDA and US EPA. Harmonizing if possible is our approach.

Regulatory counterparts: Regulation should be science based, that is important. There are many different ways to support a science – based approach. We have not arrived at a single regulatory system globally. Like-minded counterparts support a science based logical approach, and timely decision making. Industry has a role to play there too. Similar timing and decisions, and synchronous authorizations are being encouraged. For example, we may seek permission from an applicant to discuss an application with the US counterparts, which helps to coordinate a decision.

CFIA also contributes to the development of OECD consensus documents, *e.g.* cassava, even though the latter is not imported that much into Canada. Nonetheless, CFIA saw the value of providing support to the country writing the document.

Annex 1.9 Interview with USA (USDA APHIS)

Date: 9/12/2021
Organisation of the interviewees: USDA APHIS (USDA's Animal and Plant Health Inspection Service)
Interviewers: [redacted] and [redacted]

Additional questions from interviewers are given in *black italic*; answers are given in blue.

USDA APHIS has recently revised regulations for plants. In addition, USDA is currently in the process of developing a framework for the regulation of genetically engineered animals, but this is still in a very early stage.

General / Introduction

- What is the current legal framework for genome-edited organisms in South Africa, particularly for food and/or feed purposes?

In the USA, there are no laws particularly dedicated to overseeing the products of biotechnology.
The Environmental Protection Agency (EPA), Food and Drug Authority (FDA), and the USDA come across organisms/products developed with biotechnology, but rely on existing statutory authority to oversee biotechnology.

For USDA, the Plant Protection Act provides the authority a to protect from plant pests.
Former regulations were clear on product that has been developed with a vector / element from plant pest, but unclear in certain other cases.

Recently, the USDA has updated the regulations on plant pest risks. It has been a long trajectory to revise biotechnology regulations, partly due to changes in administration, with the concurrent changed views. This meant that not all efforts to revise the regulation have been fruitful. We started a third effort in 2019, and this was finalized in 2020.

An important lesson learned is that it is wise to plan a revision of legislation in in accordance with the timeframe of an administration.

- Do plants, microorganisms and animals all fall within the same framework? If not, what distinctions are made between them?

Currently, the USDA has no regulatory framework for animals, but we are contemplating it. It is under the Animal Health Protection Act, that is in place to safeguard animal health. It is still in its infancy. It will treat GE animals similar to GE plants. There have been consultations whereby comments from stakeholders and the public have been collected. We are considering what regulatory framework would be appropriate.
The experiences of the USDA with biotechnology in the USA so far, have been with plants and micro-organisms, not with animals.

GK: How about the "GloFish"?
The FDA has dealt with this, probably under the Animal Drug Act but decided not to regulate it within its enforcement discretion after a minimal data package had been provided.

- What are the main strengths of this legal framework, and what opportunities does it give?

In the setup of the regulation, the definition of genetic engineering (GE) is: the use of recombinant and/or amplified nucleic acid sequences. Within this definition fall recombinant DNA, transgenic organisms, as well as those obtained with genome editing technique, such as CRISPR-Cas.

With this legal framework, you can keep up with developments. The regulations can stay in place while technology develops. This means that you can avoid problems with revising regulations.

Within the regulation, there are several upfront exemptions for GE plants:

- Plants with changes that could also have been achieved through conventional breeding methods
  This exemption is based on experience on the one hand and scientific insights (*e.g.,* from literature) on the other. There is a history of safe use of conventional plant breeding when it comes to plant pest risks. In addition, there has been no evidence the GE techniques in themselves introduce any plant pest risk. The focus we have is on the product, rather than the process.
- A combination of a plant and a modification (same mechanism of action / trait) that has previously been assessed, so that future events are exempted under the condition that the same biochemical pathway is involved. This exemption means that we avoid cumbersome and long review processes for similar products.)

In keeping with the advances in science, these exemptions can be expanded in future through public notices. This way, rulemaking will be avoided.

When plants are not eligible for exemption, there is a petition process, with a regulatory dossier with data, from lab studies and/or field studies.
In the new regulations, this is a two step-approach. The first is to consider the plant, the new trait and the mechanisms of action underlying the trait, and to decide if there is any plausible pathway/hypothesis for the plant to be a plant pest risk. If not, than no regulation is needed. This conclusion can be based on publicly available knowledge and familiarity with the modification, hence the developer does not need to provide a lot of own data.
If there is a possible risk pathway, than a plant pest risk assessment is needed (PPRA) in the 2nd stage. For this risk assessment it might also be possible to use data that is already available, but extra, tailored data may be required as well. In that case, there is a discussion on what extra data would be required between the developer and the USDA. When the plant pest risk assessment concludes that there is no plant pest risk, no further oversight or regulation is needed.

The experience is that in many cases the developers can be informed that they do not fall under the regulation.

For the exemption on changes that have been obtained through conventional methods: are do these changes have to be present already on the market, or could they also entail modifications that could theoretically occur?
It is a mix of both. A modification that already exists within the gene pool, but was made with a biotech tool like CRISPR-Cas, this is exempted. The gene pool include plants of the same species, and plants that are sexually compatible, or that whereby re-introgression would be possible, and what is practically achievable in conventional breeding. This is because conventional breeding is considered to pose no plant risk.
The gene pool is not the same in every species – it differs what could be seen as gene pool per plant.

There are also a limited set of changes exempt that are theoretically possible, but do not exist yet: exempt when a single modification consists of:

- A change from cellular repair without a template - commonly referred to as "SDN1";
- A targeted single basepair substitution
- An inserted gene from the gene pool

A single targeted modification: very clear exemptions so they can be understood and interpretated easily. When a developer goes beyond a single change, with multiple modifications, there is the opportunity for more effects.

In the rulemaking document it is stated: modifications that were demonstrated to occur in practice are exempt whilst modifications that are only theoretical are not exempt.

Regarding the two stages procedure: is this mandatory because plants are GE, or can developers do a self determination?
Developers are able to apply the principles and assess the requirements and the exemptions themselves, there is no mandatory process for registration or notification of GE plants.
There is a voluntary procedure in place, whereby developers can seek voluntary confirmation that a plant is exempt. Non-exempted plants remain subject to the PPA.

- What are the main weaknesses of the legal framework, and what challenges do you see?

Not specifically addressed.

Definitions and scope of the regulation

- What is the definition used in legislation for the product category/-ies which encompass(es) genome-edited products? Is this definition sufficiently clear to understand whether it also covers genome-edited products? What possible ambiguity is there?

See above

- What current developments in biotechnology, if any, would not be covered by this definition? Do you foresee any in future?

Not specifically addressed.

Food and environmental safety

- What is the view on risks from genome editing? How do risks of genome-edited organisms differ from those of "traditional" genetically engineered organisms ad from conventionally obtained organisms (for example, via mutagenesis breeding)?

See above

- What risk assessments are carried out? Does it cover food and environmental safety?

See above (USDA has authority regarding plant pest risk, FDA over food safety, EPA over environmental safety)

- Unintended effects: how are these taken into account during the risk assessment?

In the EU, unintended effects are a major point of discussion. One of the viewpoints is that for plant breeding, there are regular procedures in place whereby plants with unwanted phenotypes are singled out and discarded wo they do not reach the market place, thereby making extra checks to plants redundant.
In the USA we have a similar reasoning. Unintended changes in the genome may sometimes result in phenotypic changes that were not intended. Most of these unintended changes would be removed by regular breeding procedures.
To place it in perspective, there are also many changes in the genome that happen randomly from generation to generation. We are not very concerned about unintended changes to the genome (which could also happen to the phenome).
When someone uses a genome editing technique to make edits in a plant, we want to know the strategy they use to prevent potential off-target effects in regions in the genome with close homology (such as targets that have a 1bp difference). During a review for the regulatory status, we consider the same aspect. There is no requirement for whole genome sequencing, but there is for a focus on close homologues.
In addition we consider the mode of action, to determine if there is a risk of unintended effects / additional phenotypes.

So you consider "Known unknowns" and not "unknown unknowns"?
Indeed.
In addition, we still have the authority under the Plant Protection Act to take action if there were a complete surprise to happen which turns out to be a plant pest risk. A recall action is possible.
Most of the revisions to the legislation we made, were based on experience of last 30 years. In that time frame, there were no examples of plants turning out to be a plant pest risk on hindsight.

Enforcement, detectability, and traceability

- What are the requirements for labelling, detectability, and traceability, if any? If so, who is responsible for having a detection method in place? How is enforcement and surveillance for compliance organised? (Both on products from the internal market, as well as imported products)?

Regarding the labelling component: in the US there is a clear division between regulatory oversight of GE organisms from a safety perspective, and the marketing aspect, which is not safety-related and falls within the oversight of the USDA's Agricultural Marketing Service. The information to the consumer is a market aspect and is regulated under the National Bioengineered Food Disclosure Standard, which is not safety-related. Also here an exemption is made if the same mutation could be achieved through conventional means.

- To what extent are regulated products/organisms also detectable? Can they be distinguished from products/organisms that do not fall within the scope of novel products/genetic engineering/genome editing regulations?

Regarding the regulatory science and safety regulation: those plants that are exempt and are unlikely to pose a plant pest risk, do not have a requirement for detection.

To the question if you can distinguish GE organisms, I'd say in part. You could use molecular techniques to find transgenic plants and cisgenic plants. It gets more difficult for gene edited plants, when there are plants with the same edit in the gene pool: here you could detect the edit, but not distinguish them from conventionally bred plants. In such cases, additional routes are needed for a conclusive answer.

In the US, there are many third party companies that have diagnostics to confirm presence or absence of certain components. The private sector offers solutions for those that want to market the product in a certain way.

(Economic) position& Influence on innovation

- What relationship, if any, does the regulatory framework have with your country's innovation policy? For example, does it stimulate innovation? What opportunities, if any, does it create for, for example, biotech & agrochemical companies, breeders, farmers, processors, retailers and consumers? (Compared to other countries worldwide)

There were several reasons to revise regulations, including the experience we have with biotechnology from the last thirty years, and an executive order by president to modernize the regulatory framework for agricultural biotech. The USDA is the first agency to move forward with new regulations, and the EPA is now moving forward as well. This provides relief. There is a lot of concerted effort to modernize way to look biotechnology.
The previous administration stimulated this with bi-partisan support, and now the Biden administration continues this. It also considers how biotech can be used to face challenges we face, such as those related to climate change and biofuel production.
The process of innovation is aided by regulatory predictability.

Public opinion & consumer acceptation

- How would you describe the general feeling towards biotech in your country? What difference is there in the perception of agricultural biotechnology as compared to other forms of biotechnology?

We are not aware of any USDA action towards or survey studies regarding public perception, thus it is not very appropriate to discuss this here. For the USDA it is important to ensure public confidence and that the public understands the way we do safety assessments.

The public can participate in rulemaking. For example, we publish Federal Register notices. Via this register we invite the public to review our decisions, and to give comments and point at weaknesses in case they find any. We consider this transparency on our decisions as very important.

We do consult a diverse range of stakeholders, such as academics, industry and those from the general public that happen to have an interest when we are revising our regulations, through meetings. This way, we can prevent that there are any blind spots in the process.

- Is there a different feeling towards genome editing and other new genetic engineering techniques?

Not specifically addressed

- What is likely the cause of this general view/or different views?

Not specifically addressed

- How is public perception towards the regulation?

Not specifically addressed

International harmonization:

- What aspects should be harmonized internationally in your opinion?

Not specifically addressed.

- Does your government strive towards international harmonization?

The viewpoint from the US is that we recognize that every country has their own laws for biotech products. We do have four high level goals. The first one is to convey the message that the use of biotechnology in itself does not pose safety concern, and that there is history of safe use.
The second goal is to encourage that reviews are science and risk based, to advance these fields, and to incorporate these principles under law. Many countries are adopting these principles of science and risk based assessment, and use scientific experience and developed knowledge.
The third goal is pursue cooperation and consultation, for example by sharing experiences and challenges with counterparts. The fourth is to streamline processes.
We are very willing to have conversations with regulators in the field of biotechnology worldwide, to learn from others around the world, and to give information from our perspective.

One of the challenges that remains is the operalization of regulations and the provision of a timely review. In our regulations we try to provide projected time frames. It is complex challenge to have a safe and efficient review, but it is important to have a reasonable time frame, to prevent that potential applications get stuck. By promoting harmonization of risk assessments, this can also be avoided to happen.

What experience do you have with joint reviews? In the past there was some exchange of knowledge from Canada, is something similar going on.
Our reviews are publicly available.
This topic has come up in different contexts, for example 10 years ago there was a prototype for joint review with Mexico and Canada. The experience then was that it was not saving time, as we were reviewing reviews.
Worldwide, we do see that certain countries acknowledge safety reviews performed by other countries.
It will remain a challenge to align our decisions, because of the difference in legislation.
Nevertheless the assessments can still be equivalent and we support data transportability, as well as the conversation between specialists from over the world. When experts are aligned, it releases the stress on politicians.

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