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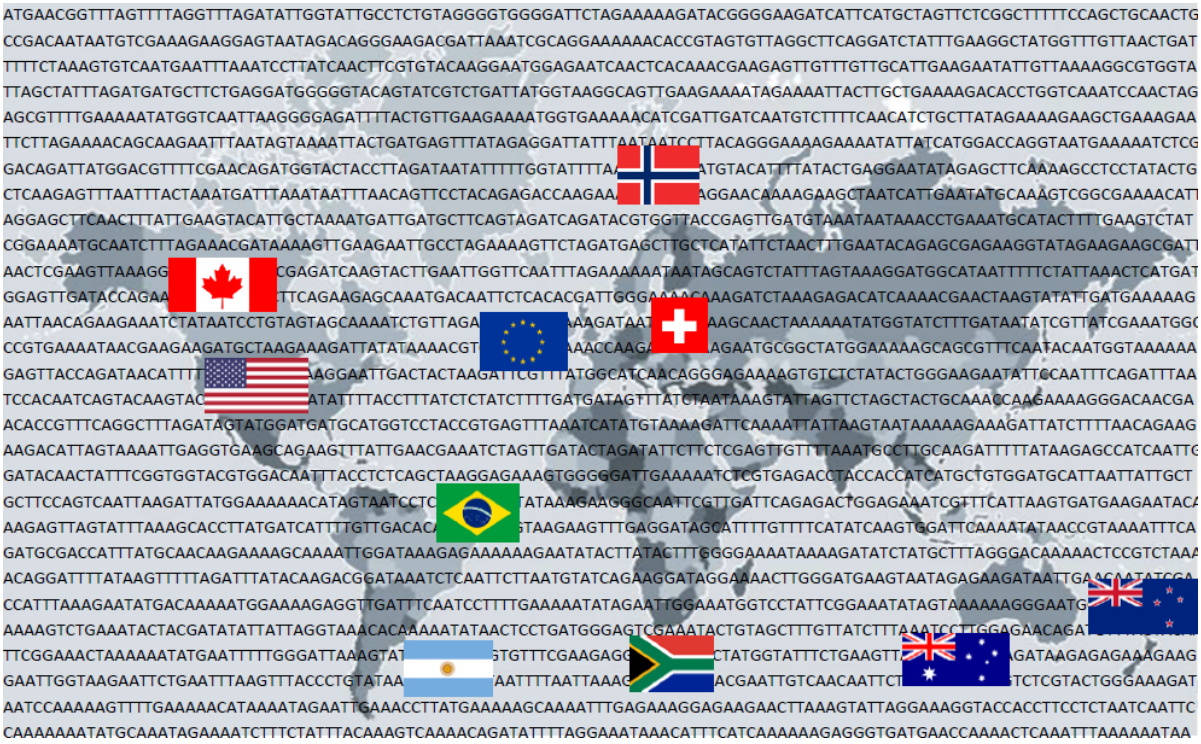
Comparison of existing Regulation Frameworks in non-EU Countries with a Focus on the respective Requirements for Risk Assessment



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Comparison of existing Regulation Frameworks in non-EU Countries with a Focus on the respective Requirements for Risk Assessment

Final report of the R&D project (FKZ: 3516 89 0400; lot3)

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Cover picture: World Map with flags indicating the countries investigated in this study in comparison to the EU, the background letters represent the DNA sequence of the Cas9 gene from *Streptococcus gordonii* (Artwork © M. Eckerstorfer)

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Abbreviations

AHPA	Animal Health Protection Act (USA)
APHIS	Animal and Plant Health Inspection Service (USA)
APVMA	Agricultural Pesticides & Veterinary Medicines Authority (Australia)
ASSAF	Academy of Sciences of South Africa (South Africa)
BCH	Biosafety Clearing House
BD	Biotechnology Directorate (Argentina)
Cas	CRISPR-associated sequence (protein)
CF	Coordinated Framework for the Regulation of Biotechnology (USA)
CFIA	Canadian Food Inspection Agency (Canada)
CFR	Code of Federal Regulations (USA)
CIBio	Internal Biosafety Committee (Brazil)
CNBS	National Biosafety Council (Brazil)
CONABIA	National Advisory Commission on Agricultural Biotechnology (Argentina)
CPB	Cartagena Protocol on Biosafety
CRISPR	Clustered Regularly Interspaced Short Palindromic Repeat
CTNBio	National Technical Commission on Biosafety (Brazil)
DAC	Department of Arts & Culture (South Africa)
DAFF	Department of Agriculture, Forestry & Fisheries (South Africa)
DEAT	Department of Environmental Affairs and Tourism (South Africa)
DNMA	Directorate of Agricultural Markets (Argentina)
DoH	Department of Health (South Africa)
DoL	Department of Labour (South Africa)
DTI	Department of Trade & Industry (South Africa)
EC	European Commission
ECJ	Court of Justice of the European Union
ECNH	Swiss Ethics Committee on Non-Human Applications of GM-Technology
EEA	European Economic Area
EFSA	European Food Safety Authority
EIS	Environmental Impact Statement (USA)
EMBRAPA	Brazilian Agricultural Research Corporation (Brazil)
ERA	Environmental Risk Assessment

EU	European Union
FAO	Food and Agricultural Organization
FDA	Food and Drug Administration (USA)
FD&C	Federal Food, Drug, and Cosmetic Act (USA)
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act (USA)
FOAG	Federal Office for Agriculture (Switzerland)
FOC	Fisheries and Oceans Canada (Canada)
FOEN	Federal Office of the Environment (Switzerland)
FOPH	Federal Office of Public Health (Switzerland)
FSANZ	Food Standards Australia New Zealand (Australia; New Zealand)
FSVO	Federal Food Safety and Veterinary Office (Switzerland)
GM	Genetically Modified
GMP	Genetically Modified Plant
GMO	Genetically Modified Organism
GRAS	“generally recognized as safe”
GTA	Gene Technology Act
HC	Health Canada (Canada)
HR	Herbicide-resistant
HSNO	Hazardous Substances and New Organisms (New Zealand)
ICGEB	International Centre for Genetic Engineering and Biotechnology
IPPC	International Plant Protection Convention
IR	Insect-resistant
LLP	Low level presence
MAGYP	Ministry of Agriculture, Livestock and Fisheries (Argentina)
MAPA	Ministry for Agriculture, Livestock and Supply (Brazil)
MN	Meganuclease
MoE	Ministry of Environment
MoH	Ministry of Health
MPI	Ministry of Primary Industries (New Zealand)
NAS	National Academies of Sciences (USA)
NBAB	Norwegian Biotechnology Advisory Board (Norway)
nGM	New Genetic Modification Techniques (in agricultural biotechnology)
NZ-EPA	Environmental Protection Agency (New Zealand)

ODM	Oligonucleotide directed Mutagenesis for Genome Editing
OECD	Organisation for Economic CO-operation and Development
OGTR	Office of the Gene Technology Regulator (Australia)
OSTP	White House Office of Science and Technology Policy (USA)
PIP:	Plant incorporated protectant
PNT	Plants with Novel Traits (Canada)
PPA	Plant Protection Act (USA)
PRA	Pest Risk Assessment
PMRA	Pest Management Regulatory Agency (Canada)
RA	Risk Assessment
rDNA	recombinant DNA
RdDM	RNA dependent DNA Methylation
RNAi	RNA-interference
RO	Release Ordinance
SAGENE	South African Committee on Genetic Experimentation (South Africa)
SAM	Scientific Advisory Mechanism of the European Commission
SDN	Site-directed Nuclease
SENASA	National Service of Agrifood Health and Quality (Argentina)
TAC	Food and Feed Safety Advisory commission (Argentina)
TALEN	Transcription activator-like effector nuclease
TSCA	Toxic Substances Control Act (USA)
USDA	US Department of Agriculture (USA)
US-EPA	Environmental Protection Agency (USA)
WHO	World Health Organisation
ZFN	Zink-Finger-directed Nuclease

Zusammenfassung

Die Entwicklung neuer gentechnischer Methoden (nGMs), welche auch als "neue (Züchtungs-)Techniken" bezeichnet werden, hat weltweit Diskussionen über die Regulierung von nGM Produkten ausgelöst. Die verschiedenen bestehenden gesetzlichen Regelwerke für gentechnisch veränderte Organismen (GVO) decken nGMs in sehr unterschiedlichem Maße ab. Die Abdeckung von nGMs hängt hauptsächlich von der Definition des regulatorischen Triggers ab. Generell lassen sich zwei verschiedene gesetzliche Definitionsansätze unterscheiden, die entweder auf das bei der Entwicklung angewandte Verfahren oder auf die Eigenschaften des entstehenden Produkts fokussieren. Eine zentrale Frage ist, ob regulatorische Rahmen, die entweder auf prozess- oder produktorientierten Definitionen von regulierten Produkten basieren, für die Regelung von nGM Anwendungen vorteilhafter sind.

In dieser Studie werden die regulatorischen Rahmenbedingungen für GVOs in verschiedenen Ländern analysiert mit Fokus auf die Regelung von neuen Anwendungen der Pflanzenzucht. Die untersuchten Gesetzesrahmen implementieren sowohl prozessorientierte als auch produktorientierte Definitionen von regulierten Produkten. Die Studie basiert auf einer Literaturanalyse und qualitativen Interviews mit Zulassungsexperten und expertInnen für Risikobewertung von GVO in den jeweiligen Ländern.

Die Prinzipien der Risikobewertung, die in allen untersuchten Ländern angewendet werden, sind einander sehr ähnlich und unabhängig von dem in den jeweiligen Gesetzen verwendeten regulatorischen Auslöser. Zusätzlich weisen beide Arten von Definitionssystemen in der regulatorischen Praxis auch Merkmale des jeweils anderen auf. Darüber hinaus zeigt unsere Analyse, dass beide Triggersysteme eine Reihe von generischen Vor- und Nachteilen haben und insgesamt keines der beiden Systeme als per se besser geeignet angesehen werden kann. Entscheidender für die Regulierung von mit nGMs hergestellten Organismen oder Produkten, sind die unterschiedlichen Kriterien, die bei der Implementation der gesetzlichen Rahmenbedingungen in den jeweiligen Ländern herangezogen werden, sowie der gesetzlichen Ausnahmen, die bestimmte nGM Anwendungen von der Regulierung ausschließen.

In einigen Ländern gibt es Diskussionen darüber, ob Änderungen der Gesetzgebung notwendig sind, um ein erwünschtes Regulierungsniveau für nGM Anwendungen zu erreichen. Wir haben fünf Strategien identifiziert, wie nGM Anwendungen in den verschiedenen Ländern in Bezug auf Biosicherheit regulieren werden - von der Anwendung bestehender Rahmenbedingungen für die Biosicherheit ohne weitere Änderungen bis hin zur Schaffung neuer eigenständiger Rechtsvorschriften für nGM Produkte. In einigen Gesetzgebungen, darunter auch Neuseeland und die EU, wurde mittels Gerichtsentscheidungen über den Regulierungsstatus bestimmter nGM Anwendungen entschieden, insbesondere über die Methoden der gerichteten Mutagenese (Genomeditierung). Nach der diesbezüglichen Rechtsprechung fallen solche Anwendungen in beiden Rechtsordnungen unter die bestehenden Regelwerke zur Biosicherheit. Andere Länder, darunter Argentinien, Brasilien und Australien, haben Änderungen ihres regulatorischen Rahmens vorgeschlagen und/oder verabschiedet, die bestimmte Ansätze zur Genomeditierung von der Regulierung durch ihre Biosicherheitsvorschriften ausnehmen.

Aufgrund der unterschiedlichen Ansätze bei der Regulierung von nGM Anwendungen wird eine internationale Harmonisierung in naher Zukunft vermutlich nicht erreicht werden

können. Im Kontext des internationalen Handels ist aber Transparenz über den Regulierungsstatus einzelner nGM Produkte von zentraler Wichtigkeit. Wir schlagen daher die Einführung eines internationalen Registers vor, in dem alle in der Landwirtschaft kommerziell genutzten biotechnologischen Produkte, darunter auch alle nGM Anwendungen, erfasst werden. Dieses Register sollte insbesondere jene nGM Produkte umfassen, die unter die in der EU geltenden Gentechnikregelungen fallen und ausreichende Informationen enthalten, um die jeweiligen nGM Produkte mit analytischen Methoden eindeutig nachweisen zu können.

Die wichtigsten Ergebnisse dieser Studie sind in ECKERSTORFER et al. (2019a) veröffentlicht. Um mögliche Widersprüche zu vermeiden sind die entsprechenden Textpassagen und Tabellen identisch.

Summary

The development of new genetic modification techniques (nGMs), also referred to as “new (breeding) techniques” in other sources, has raised worldwide discussions regarding their regulation. Different existing regulatory frameworks for genetically modified organisms (GMOs) cover nGMs to varying degrees. Coverage of nGMs depends mostly on the regulatory trigger. In general two different trigger systems can be distinguished, taking into account either the process applied during development or the characteristics of the resulting product. A key question is whether regulatory frameworks either based on process- or product-oriented triggers are more advantageous for the regulation of nGM applications.

We analysed regulatory frameworks for GMOs from different countries covering both trigger systems with a focus on their applicability to plants developed by various nGMs. The study is based on a literature analysis and qualitative interviews with regulatory experts and risk assessors of GMOs in the respective countries.

The principles of risk assessment applied in all investigated countries are very similar independent of the regulatory trigger used in the respective pieces of legislation. Even though the regulatory trigger may be either process- or product-oriented or a combination thereof, both types of trigger systems show features of the respective other in regulatory practice. In addition our analysis shows that both trigger systems have a number of generic advantages and disadvantages, but neither system can be regarded as superior at a general level. More decisive for the regulation of organisms or products, especially nGM applications, are the variable criteria used to implement the triggers in the different regulatory frameworks as well as exemptions excluding certain nGM applications from existing legislation.

There are discussions and consultations in some countries about whether changes in legislation are necessary to establish a desired level of regulation for nGM applications. We identified five strategies for countries that desire to regulate nGM applications for biosafety - ranging from applying existing biosafety frameworks without further amendments to establishing new stand-alone legislation. In some legislations, including New Zealand and the EU court decisions were sought to decide on the regulatory status of certain nGM applications, namely directed mutagenesis methods (genome editing). According to the respective rulings such applications are covered by the existing regulatory frameworks for biosafety in both jurisdictions. Other countries, including Argentina, Brazil and Australia introduced and/or adopted amendments to their regulatory framework which exempt certain approaches for genome editing from oversight according to their biosafety laws.

Due to the different approaches towards the regulation of nGM applications, international harmonisation will supposedly not be achieved in the near future. In the context of international trade, transparency of the regulatory status of individual nGM products is a crucial issue. We therefore propose to introduce an international public registry listing all biotechnology products commercially used in agriculture. This registry should include all nGM applications, which are covered by the current regulatory system in the EU and contain sufficient information to enable the unequivocal detection of the respective nGM products by analytical methods.

The main results of this study are published in ECKERSTORFER et al. (2019a). To avoid misunderstandings respective text passages and tables are identical.

1 Introduction

Genetically modified organisms (GMOs), like genetically modified (GM) crop plants, are regulated in most countries by specific legal frameworks. While the respective regulations are different to various extents e.g. regarding the scope, the individual provisions and the involved authorities; most of these regulatory frameworks share some common principles and approaches, e.g. they build on the fundamental principles for food & feed safety and the environmental risk assessment of crops produced by modern biotechnology developed by international bodies like the FAO/WHO and the OECD (JONES 2015a).

The subject addressed by the different national regulations typically is the modified organism generated by the GM technology, i.e. the "product" generated by the technology.

However different approaches were developed to "trigger" regulatory action, i.e. to determine whether a specific organism is regulated by the respective legal framework or not:

- Some countries adopted definitions, which are based on characteristics of the process used to generate GMOs. These approaches focus on characteristics of the GM technology and are commonly described as "process-oriented" approaches to trigger regulation.
- Other approaches rather focus on specific characteristics of the GM product and its intended purpose of use, and not on the process by which the GM product is created. These approaches are typically referred to as "product-oriented" triggers of regulation. The specific characteristics triggering regulatory action are biological traits that are typically associated with adverse effects, e.g. a potential to exhibit pathogenic behaviour or weediness, or the "novelty" of a specific product.
- A third category of approaches can be described as "risk-oriented"; risk-oriented regulations address organisms, which may exert adverse effects on humans, animals and the environment under the conditions of the intended use. Typically risk-oriented systems rely on case specific considerations to determine whether the risks associated with a certain organism should trigger regulatory action or not.

However a clear differentiation sometimes may not be feasible since the above mentioned "triggers" are also used in a combined way in specific regulatory frameworks. In addition process-oriented and product-oriented systems are characterised by an implicit general consideration that certain risks may be associated with the application of specific biotechnological methods or certain product characteristics.

At the EU level a trigger defining what is considered a GMO and therefore subject to regulation is provided by Directive 2001/18/EC on the Deliberate Release into the Environment of GMOs, which was transposed into the national regulations implemented by the EU member states. GMOs according to the definition are - among other provisions - subject to a mandatory notification procedure and have to undergo a risk assessment prior to authorisation for environmental release and/or placing on the market. The definition hinges on characteristic aspects of the GM technology (also referred to as recombinant DNA-technology or genetic engineering) used to generate regulated products. The regulatory trigger at the EU-level as well as in the corresponding legislation of EU member states is therefore considered to be process-oriented (KRÄMER 2015, SPRANGER 2015). However,

according to other interpretations the definition in the EU Directive is considered to be both process- as well as product-oriented (KAHRMANN et al. 2017).

On an international level the Cartagena Protocol on Biosafety (CPB) provides a reference definition of living organisms produced by techniques for genetic modification (CPB 2000)[1]. Various national regulations are following this definition. The definition provided by the CPB of living modified organisms (LMOs) developed by GM technology is comparable to the definitions for GMOs implemented in the EU legislation and in regulations which exist in the EU member states.

Some countries, like Canada and the USA, established product-oriented regulatory systems which mainly focus on characteristics of the products rather than on the specific methodology used to create these products (SCHUTTELAAR 2015). Typically genetically modified organisms, which are subject to the EU regulation framework for GMOs would also be covered by such regulations.

However in recent years a diverse range of biotechnological approaches was developed, which are different in methodology from both mutation breeding and from classical GM technology. These approaches to modify the genome and/or the traits of living organisms, among others crop plants, are commonly known as “New Techniques” (LUSSER et al. 2012), SAM (2017). For the purpose of clarification and to avoid the possible misconception on the part of non-experts that these technologies are just variants of conventional cross-breeding methods we prefer to use the term “new genetic modification techniques” (nGMs) instead (ECKERSTORFER et al. 2019a). As a number of different techniques is included in the nGM group of methods, there is still regulatory uncertainty how to address some of the nGM approaches under the current EU regulatory framework. In some EU member states, e.g. Germany, UK, the Netherlands and Sweden, developers have approached the authorities with requests to determine the status of different plants developed by genome editing (BVL 2015, JANSSON 2018). These decisions, e.g. concerning herbicide resistant oilseed rape lines developed by ODM, were based on an interpretation of the GMO definition given in Article 2 of Directive 2001/18/EC which argues that the expression “ … *organism, … , in which the genetic material has been altered in a way that does not occur naturally …”* refers to the characteristics of the genetic modifications in the final product rather than to the methods used for genetic modification (BVL 2015, KAHRMANN et al. 2017, SPRINK et al. 2016a). However these decisions were taken prior to the ruling of the Court of Justice of the European Union (ECJ) in July 2018 on applications of directed mutagenesis. The ECJ determined in its ruling that applications of directed mutagenesis are covered by the regulatory trigger implemented by Directive 2001/18/EC in the EU and also ruled that they are not exempted according to Article 3, Para 1 and Annex 1B of the Directive. The court concluded that the exemption of mutagenesis methods referred to in Annex 1B does not apply to the introduction of genetic modifications by nGMs like genome editing, since the risks linked to the use of those new genetic modification techniques/methods of mutagenesis might prove to be similar to those which result from the production and release of a GMO through transgenesis (ECJ 2018). The ruling confirmed that a general exemption of new methods for mutagenesis would not be in line with obligations for regulatory oversight and

[1] Article 3 (g) "Living modified organism" means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology.

risk assessment in accordance with the precautionary principle enshrined in European legislation. Consequently any previous decisions taken by authorities of EU member states have been reviewed and repealed when not in line with the ECJ ruling.

The differences in the definitions implemented for applications of modern biotechnology in non EU regulations and their interpretation by national authorities govern whether certain nGM applications are subject to these regulations or are exempted from requirements according to these regulations. Such decisions do also result in either requirements for a risk assessment prior to marketing or a preliminary check by authorities whether a full risk assessment is required for a specific nGM application.

2 Regulation frameworks addressed in this study

2.1 Countries selected for analysis

The following countries were selected for comparison with the current situation in the EU:

- Norway
- Switzerland
- USA
- Canada
- Argentina
- Brazil
- Australia
- New Zealand
- South Africa

This selection was based on the following considerations:

- The chosen countries implement different regulatory systems which were either developed in a national process based on the existing constitutional and general legislative framework or which are based on or widely compatible with the CPB.
- The different analysed regulatory frameworks therefore are comparable to the existing EU-regulations to varying degrees. A common feature to all of these regulatory frameworks, however, is the requirement that a risk assessment is conducted prior to authorisation of use of regulated GM products.
- The selected regulation frameworks are implementing different regulatory triggers or definitions which biotechnological products are subject to the specific legislation and its biosafety-related requirements.
- The range of analysed regulations includes countries which use different process-oriented definitions to trigger regulatory action (i.e. EU- and European countries, South-American countries, Australia and New Zealand), as well as different product-oriented triggers (i.e. both North American countries).
- The selected countries actively implement these regulations with a substantial history of experience, particularly for the regulation of different applications of GMOs, including plants for agricultural use and for different scopes of use, e.g. confined release for field testing, import and processing of GM products and unconfined environmental release, including commercial cultivation of GM crop plants. Some of the chosen countries are among the main producers and exporters of agricultural GM products (USA, Canada, Argentina, Brazil, Australia).
- The selection also considered whether the respective countries were exposed to the question if nGM applications would be subject to their biosafety laws or not. Most of these countries have scientific or commercial stakes in the development of different nGM applications (including plants developed by nGMs) or in their (agricultural) use.

Some of these countries actively discussed or discuss whether specific regulations should be developed for nGM applications or existing regulations should be updated with a view to the challenges presented by nGMs.

2.2 nGMs considered in this study

The study at hands addresses inter alia the question how different nGMs would be treated according to the regulatory frameworks existing in the countries outlined in chapter 2.1. Therefore a number of nGMs was selected for the analysis, which cover the range of techniques currently in development or use (SAM 2017, VOGEL 2016). Additionally the selected nGMs should be representative for the challenges which are posed by nGMs regarding regulatory questions or questions related to biosafety and risk assessment.

Since no accepted definition exists which biotechnological methods are considered to be nGMs, the following list of nGMs is used in the framework of this study. The list includes nGMs addressed by the deliberations of the EU working group on new techniques (i.e. nGMs) (NTWG 2012) and the accompanying study by the Joint Research Centre of the European Commission on the subject (LUSSER et al. 2011), as well as the report of the scientific advisory mechanism to the European Commission (SAM 2017).

Table 1: Overview on the nGMs addressed in this study

Category	**nGM**	**Specific nGM approach**
Genome editing with Site Directed Nucleases (SDN)	CRISPR-based systems for genome editing	SDN-1 SDN-2 SDN-3 Base editing
	Transcription activator-like effector nuclease (TALEN)	SDN-1 SDN-2 SDN-3
	Zinc-Finger-directed nuclease systems (ZFN)	SDN-1 SDN-2 SDN-3
	Meganuclease-based systems (MN)	SDN-1 SDN-2 SDN-3
Genome editing by oligonucleotides	Oligonucleotide directed Mutagenesis (ODM)	-
	Multiplex Automated Genomic Engineering (MAGE)	-
Modification of gene expression	RNA dependent DNA Methylation (RdDM)	-

	Other techniques for the modification of gene expression	Virus-aided gene expression (VAGE) RNAi-based gene silencing CRISPR-based modification of gene expression
	Cisgenesis/Intragenesis	Cisgenesis Intragenesis
	Transgrafting	Grafting on GM Rootstock
	Agroinfiltration	Agroinfiltration Agroinfection Floral Dip
	Haploid Induction (HI)	CenH3-based HI
	Reverse Breeding	-

The listed nGMs are further described and characterised concerning risk issues in ECKERSTORFER et al. (2019b).

2.2.1 **Characteristics of the nGMs addressed in this study**

The list of nGMs presented in Table 1 represents different types of nGMs regarding

- the underlying technologies and the objectives for their application,
- the types and scopes of modifications, which are introduced by their application and
- the question whether the modifications introduced by the respective nGMs are comparable to modifications resulting from either classic GM technology or methods used in conventional plant breeding approaches.

The nGMs addressed in this study encompass a set of techniques developed to serve different purposes: The respective nGMs are used first as tools e.g. in scientific research, secondly as means to support and improve classical plant breeding approaches and third for the development of specific traits in plant breeding.

- Some of these nGMs, e.g. approaches for genome editing (SONGSTAD et al. 2017), cisgenesis and intragenesis, and approaches to modify the expression of endogenous genes like RNA-dependent DNA-methylation (RdDM) and RNA-interference (RNAi), are used to introduce specific heritable modifications, to obtain desired phenotypes. The respective modified plants are intended to be used in agriculture and/or food and feed production.
- Another group of nGM applications, e.g. agroinfiltration and transgrafting are used to modify only somatic parts of the respective plants and create chimeric plants which consist of parts that are genetically modified and non-modified plant parts. The respective modifications are usually not passed on to offspring produced from the modified plants, but properties of non-modified plant parts may be influenced by effector substances produced in modified parts and spreading through the whole plant.

- Other nGMs like haploid induction (HI) (RAVI&CHAN 2010), reverse breeding (RB) or accelerated breeding (AB) (SCHAART et al. 2016) are predominantly used to facilitate and/or speed up specific breeding processes. The resulting plants developed by these nGMs are meant to be free from any transgenes and other genetic modifications that were introduced during the breeding process.

These nGMs facilitate the introduction of different types of molecular modifications into recipient plants at the genetic and/or epigenetic level. Broadly speaking the following 4 classes of modifications may be distinguished:

1. Heritable insertion of transgenic DNA into the final breeding product:
   Some of the covered nGMs like cisgenesis, intragenesis, RNAi-applications in plants and transgrafting are based on stable insertions of recombinant DNA constructs into the genome of a recipient plant. Some genome editing-approaches which are commonly referred to as SDN-3 (type 3 Site-Directed Nuclease applications) facilitate the insertion of transgenic constructs at specific genomic locations. In most of the mentioned nGM applications the respective transgenic insertions are present in a heritable way in the final breeding product; only with transgrafting applications using GM-rootstocks these transgenic modifications cannot be passed on by sexual reproduction.
2. Transient introduction of transgenic DNA:
   Transgenic constructs are also present in breeding intermediates for other nGM-approaches (e.g. transgenic constructs required for RdDM, HI, RB and AB, and transgenic nuclease expression constructs for genome editing-approaches). These transgenic insertions, however, are removed in final breeding steps and supposed to be absent from the final breeding products. In other nGMs like agroinfiltration recombinant DNA constructs are only present in the treated plants for a certain time without an intention to result in the genomic insertion of transgenes.
3. Genome Editing:
   Genome editing-approaches based on SDNs and oligonucleotide-directed Mutagenesis (ODM) lead to random (SDN-1) or specific sequence changes (SDN-2 and ODM) at predefined genomic loci. The latter are directed by the sequence of synthetic nucleic acids, which are also introduced into the recipient plant cells in the course of the respective nGM procedure. Base-editing approaches using CRISPR-Cas-based tools facilitate the conversion of specific nucleic acid bases at the targeted genomic loci (MATSOUKAS 2018). In all cases a desired modification can afterwards be selected from a collection of mutagenized plants harboring different mutant alleles. This is particularly relevant for SDN-1 approaches of genome editing in plants.
4. Epigenetic Engineering:
   Other nGM approaches like RdDM and site-specific methylation/demethylation using CRISPR-based tools lead to the modification of epigenetic regulation signals in the modified plants, rather than to a modification of their genomic DNA-sequence (CHANGQING ZHANG 2013, PUCHTA 2016).

2.2.2 **Risk assessment considerations for nGM applications**

General considerations

According to the recommendations drawn in the recent EU-level report “New Techniques in Agricultural Biotechnology” (BUJNICKI 2017) the risk assessment of environmental effects needs to consider all of the following issues:

- Effects due to intended changes present in the modified plant
- Effects due to unintended changes present in the modified plant
- Effects due to characteristics of the modified plant species and its interaction with the receiving environment
- Effects due to the intended use of the modified plant and the resulting exposure of the environment

An appropriate assessment should be based on a comprehensive assessment of the effects of the intended traits as well as on a careful analysis of the whole plant for unintended effects of all possible modifications, similarly as for GM plants (EFSA 2010, VAN HAVER 2008). As elaborated in ECKERSTORFER et al. (2019b) the overall risk assessment approach for nGM applications needs to be based on two types of considerations:

1. Trait related considerations
2. Technology related considerations

Trait related considerations

Relevant for the evaluation of effects associated with intended traits in nGM plants is whether experience with such traits is available from the previous use of similar or comparable traits in plants already in use in agriculture and for food and feed production. However such information is not always available, since a significant number of genetic changes by nGMs result in the expression of modified gene products without a documented history of safe use.

The survey of the recent literature provided some indications towards the traits which are or may be developed in the near future using the different nGMs. As described in ECKERSTORFER et al. (2019b) some groups of traits are specifically relevant:

- Traits eliciting herbicide resistance (HR) in crop plants:

HR are developed mostly by genome editing and less frequently by cisgenesis and intragenesis: this group includes traits for resistance against a number of classes of broadband-herbicides (e.g. Imamazamox™/Chlorsulfuron™, glyphosate-based herbicides, glufosinate, Tembotrione™ or Quizalofop™). This is achieved by modification of the respective plant enzymes to resist inhibition by these herbicides.

Experience with effects resulting from these traits is available from the RA of GM plants with comparable traits. Relevant are in particular indirect effects resulting from the changes in weed management, and the development of herbicide resistant weeds (EFSA 2010). The dispersal of HR volunteer plants like oilseed rape and the persistence of such HR volunteers leading to an increase of herbicide use in subsequent crops were identified as major concerns for HR crops developed by conventional breeding (EXPERTGROUP 2014).

Furthermore other pleiotropic effects need to be considered which are associated with some of the HR-genes which are present in nGM applications. E.g. overexpression of EPSPS genes resulted in an elevated auxin content and an increased fecundity of the modified plants (FANG et al. 2018).

- Traits resulting in compositional changes in the modified plants:

A variety of different traits was developed mostly by genome editing-approaches and some by cisgenesis/intragenesis. Examples for targeted traits were among others: changes to sugar and starch content, altered lipid composition, reduced content of lignin, browning agents, phytate in different plants and of components which reduce processing quality and storage ability of seeds, elimination of allergenic and antinutritive components in soybeans and wheat, and enhanced content of substances increasing fragrance in rice.

Based on experience with problem formulation for the RA of GM plants a number of potential risk issues regarding food and feed safety and environmental effects should be addressed in the RA (EFSA 2011b).

- Traits for resistance to diseases caused by a variety of plant pathogens:

A number of different approaches were developed for increased resistance of plants against different viral, bacterial and fungal pathogens. Approaches included silencing of viral genes through RNAi in transgrafting applications, knock-down of plant susceptibility factors by genome editing-approaches, expression of resistance genes and antimicrobial substances by transgrafting and cisgenesis applications.

For fungal resistance due to knock-out of plant susceptibility genes a number of pleiotropic effects such as reduced plant size or premature senescence were described (KUSCH&PANSTRUGA 2017). For applications to induce virus resistance by transgrafting concerns which should be addressed by RA have been identified by LEMGO et al. (2013). These include pleiotropic silencing effects, effects of the transgenic rootstock on non-target organisms, e.g. on soil organisms, gene transfer of virus-resistance to wild type plants and effects on fitness and invasiveness, potential development of novel viral strains and food safety effects.

- Traits for enhanced fitness against environmental stressors and for the alteration of morphological or reproductive characteristics of the modified plants:

Several approaches including genome editing-applications and transgrafting aim to establish a variety of different traits with environmental/ecological relevance: abiotic stress response (e.g. to cold, drought,), alteration of symbiotic nitrogen fixation, altered composition of secondary cell wall, male sterility, modulation of flowering onset or flowering time, increased shatter resistance of seed (oilseed rape), early maturation and facultative parthenocarpy.

Such traits need to be assessed for adverse effects related to enhanced fitness and the resulting ecological effects, e.g. an increased potential for invasiveness or weediness. Also the potential transmission of modified reproductive characteristics to related species needs to be assessed as this may result in negative environmental effects due to a possible decrease in the reproduction of valued species or an increase in the reproduction capabilities of weedy species.

Technology related considerations

Unintended molecular changes may be conferred to nGM plants by effects associated with the nGM mechanism or with any other biotechnological method which needs to be applied for the successful development of the respective nGM applications. These molecular changes may lead to undesirable phenotypic effects.

The following issues are relevant regarding method-related effects:

- Molecular changes associated with methods for genetic transformation or introduction of nGM-related components (nucleic acids, (ribonucleo-)proteins) into the recipient cells:

Some commonly used transformation and transfer systems may increase the rate of unintended mutations (LATHAM et al. 2006). Some of these transformation techniques are also associated with unintended molecular changes at the genomic integration site upon insertion of the recombinant constructs.

- Unintended off-target effects associated with the nGM mechanism:

Some nGMs are known to be associated with unintended effects, e.g. genome editing-approaches can be associated with off-target effects. The available information on the probability of nGMs to result in such off-target effects and on their possible location may be used to specifically screen for off-target effects (including deletions, insertions, genetic rearrangements, mobilisation of transposable elements, etc.) (YEE 2016). However an exhaustive and unbiased general screening for genome wide off-target effects is not conducted routinely. It also needs to be addressed which specific adverse effects may be associated with such off-target changes.

- Other unintended effects associated with the introduced genetic modifications:

Pleiotropic effects (e.g. toxicological or allergenic effects), positional effects or epigenetic changes may be associated with the molecular changes which are introduced by nGMs. A molecular characterization can provide indications as to which effects may be expected, whether these effects are stable and whether any transgenic method-related constructs/components inserted in intermediate breeding steps are still present in the final breeding product.

- Unintended modifications associated with (biotechnological) methods for tissue- or cell-culture are used for transformation and regeneration:

As summarised by HCB (2017) cell-culture and regeneration can lead to genetic and epigenetic modifications which may result in unintended phenotypical effects. Of particular interest are therefore the following issues: Are protoplast-based methods or substances with mutagenic or hormonal effects used during culture? To which extent are the somatic mutations introduced during (cell) culture eliminated by the breeding process?

All above issues should be addressed by an appropriate molecular characterisation of the nGM application and documentation of the procedures which were used to establish the nGM application in question. Information from the molecular characterization can then be used to assess the probability of unintended effects and to predict potential effects at the phenotypic level.

2.2.3 Aspects relevant for risk assessment considerations regarding nGM applications

The following aspects are of particular relevance regarding risk assessment considerations for nGM applications:

- The level of experience with specific nGM applications
- Different sources of possible risks due to combination of different biotechnological techniques
- The range of plant species which may be modified by nGMs and of the traits developed in the modified plants

The level of experience with specific nGM applications

Relevant for risk assessment considerations is the level of understanding concerning the mechanisms on which the particular nGMs are based. Furthermore experience regarding optimization of their application and the availability of information on unintended effects which may be associated with the techniques is relevant. The knowledge base is highly variable among nGMs; for many nGMs the existing experience is still limited due to recent introduction or limited number of applications. Similar limitations can be noted regarding the understanding of the biological mechanisms underlying the techniques as well as their potential unintended effects (ECNH 2016).

Different sources of possible risks due to combination of different biotechnological techniques

The specific nGMs may not be evaluated in isolation, since practical experience demonstrates that most nGM applications are based on a combination of different biotechnological methods, including GM methods, e.g. to transfer and express the molecular tools for the respective nGMs. For some nGM approaches techniques of cell cultivation and regeneration which are known to result in unintended genetic changes have to be used in the overall breeding process. Protoplast culture and regeneration e.g. need to be applied for genome editing-applications which are based on introduction of active (ribo)nuclease-components into the target cells. Such approaches were developed in recent years as an alternative to the transgenic modification of plant cells for the expression of the different types of nucleases needed for genome editing approaches.

The range of plant species which may be modified by nGMs and of developed traits

A survey of the recent literature addressing nGM applications in plant science demonstrates that an extremely wide range of plant species was used in relevant research and development projects: The range does comprise model species for research (like Arabidopsis and tobacco), most crop species including all major crops like maize, rice, wheat, soybean, etc., plants used for oilseed production and legumes, vegetable and spice plants, perennial plants including fruit trees and forest trees as well as lower plants, like moss species.

Similarly the range of intended traits which are developed by nGMs is very broad: The scope includes trait categories with a high relevance for agronomical application like traits for herbicide resistance, traits resulting in compositional changes, traits for resistance against a variety of pathogens, traits for enhanced environmental fitness including stressors like cold,

draught and salinity and for changes of morphological and reproductive characteristics including early flowering.

2.3 Aspects considered during evaluation of the different regulatory frameworks

The legislation from the countries outlined above are evaluated regarding the following aspects:

- Main features of the regulatory framework for biotechnology applications
- Degree of coverage of nGM applications by the respective legislation
- Risk assessment requirements according to the legislation

The evaluation is directed to address a number of particular questions for each of the above mentioned aspects.

2.3.1 **Main features of the regulatory frameworks**

- Which legislation specifically addressing biotechnology applications exists in the country in question?
- Which range of biotechnology applications is subject to specific legislation (scope of existing legislation)?
- When were the respective legislation introduced and amended?
- Which authorities are involved in implementation of specific legislation?
- Which approach to regulation is implemented (is regulation triggered by process-oriented considerations, product-oriented considerations, risk- or novelty-oriented considerations or a combination of different aspects)?
- Does the legislation require a risk assessment prior to authorisation of products for environmental release (field testing: import of materials, e.g. for commercial food or feed production; cultivation of modified crop lines)?

2.3.2 **Coverage of nGMs by the regulatory frameworks**

- Is specific legislation for nGM applications in place, or are nGM products covered by other existing legislation, in particular by GMO legislation?
- Is new legislation currently being developed for nGMs and what is the scope of the new legislation?
- Which nGMs are subject to regulation (included by definition, or based on case-by-case decisions)?
- How are nGMs regulated which are not covered by existing GMO-legislation?

2.3.3 Risk assessment requirements for GMOs and nGM applications

- Is a pre-evaluation of possible risks required to determine regulatory status of a specific nGM application?
- Are comparable standards for risk assessment implemented for GMOs and nGM applications?

To highlight outstanding aspects for each of the analysed regulatory frameworks all chapters addressing country information contain a bulleted list of aspects, which are considered to be of particular importance by the authors of the study. It should be noted, that these lists are not meant to be exhaustive summaries of the preceding chapters.

2.3.4 Outstanding aspects of the existing regulation frameworks

At the end of each chapter addressing country-specifics a short summary is provided with some take-away messages selected from the country information.

2.4 Sources of information considered for analysis of regulatory frameworks

Different sources were used to compile the information summarized in the respective subchapters on individual countries (see chapter 3).

- First of all relevant pieces of existing legislation were used for reference, e.g. regarding definitions of regulated items, regulatory procedures and requirements, involved authorities, and assessment criteria.
- Second, the available scientific literature and previously published reports concerning the subject matter of this study were taken into account.
- Third, additional information was gathered from interviews performed with experts on regulatory matters from the respective countries. Further information concerning these interviews is presented in the following subchapter 2.4.1.

2.4.1 Interviews with regulatory experts

To supplement the available published information in-depth interviews were conducted with experts from non-EU countries included in this study. The selected experts are involved in the respective national GMO regulation in different capacities, e.g. as regulators, members of institutions or committees involved in risk assessment of GM applications or stakeholders with a high familiarity with the respective legislation and its implementation. The interview partners answered the questions in their personal capacity. In a few cases appropriate interview partners could not participate due to different reasons (e.g. availability, lacking national consent to discuss ongoing internal regulatory review processes publicly).

A common questionnaire was used to conduct the interviews. The questions were aimed to establish a better understanding of the different regulatory approaches and to learn from experiences gathered in other countries with the practical implementation of the respective regulations. The questionnaire is included as Annex 1 of this report. Depending on the current situation in the respective countries, not all questions were equally relevant for all countries and/or could not be addressed by the interview partners. Answers were used as

further input to the respective subchapters of chapter 3. The questions addressed two general issues:

a) Questions Part 1: Aspects of the existing system developed for GMO regulation in a respective country, in particular:
    - How is the regulation "triggered", i.e. which characteristics of the resulting products or biotechnology techniques used are relevant to determine whether a certain application is regulated or not (e.g. is a process-oriented or product-oriented trigger used)?
    - Which risk assessment requirements according to the existing biosafety regulatory framework apply for regulated items?
b) Questions Part 2: Issues related to the regulatory treatment of emerging biotechnology-/nGM applications:
    - Which regulatory approach is developed or implemented for nGM applications?
    - Which risk assessment requirements will be applied for nGM applications?

3 Country-specific information

3.1 European Union

3.1.1 Main features of the EU regulatory framework

Existing legislation

The EU system for GMO-authorization is based on three core legislative documents, laying down the authorisation procedure and the requirements which need to be fulfilled by the applicant: Directive 2001/18/EC for deliberate release and placing on the market of GMOs, Regulation (EC) No 1829/2003 for GM food and feed and Directive 2009/41/EC for contained use of genetically modified micro-organisms. These are supplemented by a large number of additional regulations, directives and other legal documents laying down detailed rules for implementation (e.g. for co-existence, traceability or risk assessment).

This regulatory framework is implemented in different ways: while the authorisation of experimental field trials using GMOs and contained use of GM microorganisms is in the competence of the member states, commercial use (cultivation and food/feed use) of GMOs requires authorization by the EU.

Authorities involved in the authorisation process

The responsibilities for national authorisation (field trials and contained use) vary depending on the respective member state. Member states have one or more national competent authorities, e.g. the ministry of health, environment or agriculture, usually one leading the authorisation process for a specific application. In many cases other ministries, agencies and a scientific biosafety committee or advisory body are involved. The final decision is taken by the designated competent authority.

For EU wide authorisation the detailed procedure depends if the GMO is authorized for cultivation and non-food/feed use only following Directive 2001/18/EC or for GM food/feed (import and cultivation) following Regulation (EC) No 1829/2003.

However, in both cases the general procedure is similar: the only main difference is which institutions are responsible for the mandatory risk assessment: The applicant has to send the application to a member state. Following the Directive 2001/18/EC, this member state is also responsible for carrying out the risk assessment, involving all other member states, and drafting the final opinion, which is then sent to the European Commission. In case objections are raised by other member states an EU level assessment is conducted under the authority of the European Food Safety Authority (EFSA).

For notifications according to Regulation (EC) No 1829/2003, the member state sends the application to EFSA which is responsible for checking the documents for completeness and for carrying out the risk assessment, supported by a specific scientific panel (GMO panel of experts). In accordance with Article 6 of Regulation (EC) No 1829/2003 the EFSA may ask a member state's authority to carry out the risk assessment for food, feed and the environment. In case the application does also concern GMOs to be used as seeds or other plant-propagating material, EFSA shall ask a national competent authority to carry out the environmental risk assessment. All member states have access to the application and can, but are not obliged to, send their comments to EFSA. The final opinion is prepared by EFSA, taking the comments from member states and, if applicable, the risk assessments carried out

by member states according to Article 6 of Regulation (EC) No 1829/2003 into account. This final opinion is then sent to the European Commission. In both cases the European Commission publishes a draft decision which is then voted upon in the Council. If no qualified majority in favour or against the authorisation is reached, the Commission decides on the authorisation following its original proposal.

The main difference between these two procedures is that the responsibility for handling the application and the preparation of the final opinion under the Directive 2001/18/EC is with the member states (decentralized approach) and under the Regulation (EC) No 1829/2003 with EFSA (centralized approach).

Regulatory approach

The basis for GMO regulation is the definition of a GMO given in Article 2 of Directive 2001/18/EC:

"*Genetically modified organism (GMO) means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination*."

However the Directive also specifies a closed list of exceptions in its Annex 1B:

"Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are:

(1) mutagenesis,

(2) cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding methods."

Following the definition of a GMO and the exceptions, the regulatory system is triggered by the way an organism has been developed ("process trigger") and not by its properties ("product trigger"). Therefore herbicide resistant crops, which have been created by conventional breeding, even if it involved mutagenesis by e.g. applying radiation or chemical mutagens, are not regulated under GMO legislation and not subject to authorisation.

3.1.2 Coverage of nGMs by the EU regulatory framework

The coverage of nGMs by the GMO legislation has been under discussion for several years. Already in 2009 the European Commission installed a first expert working group and announced to publish a legal opinion based on the results of this working group. However, the mandate of the expert group has been extended and the legal opinion has been delayed several times. In 2017 a report by the Scientific Advisory Mechanism of the EU/EC was published (SAM 2017). However, this report focused on technical and scientific issues and did not contribute to clarify regulatory issues.

The European Commission has not initiated any activities to this regard before the judgement of the Court of Justice of the European Union (ECJ) regarding a preliminary ruling is issued, which has been referred to the ECJ by the French Conseil d´État. The judgement issued in 2018 clarified that directed mutagenesis techniques are also included in the

definition of a GMO according to Directive 2001/18/EC and that such approaches of genome editing are not exempted according to Article 3, Para 1 and Annex 1B of the Directive. The court further concluded that the exemption of mutagenesis methods referred to in Annex 1B does not apply to the introduction of genetic modifications by nGMs like genome editing, since the risks linked to the use of those new genetic modification techniques/methods of mutagenesis might prove to be similar to those which result from the production and release of a GMO through transgenesis (ECJ 2018). The ruling confirmed that a general exemption of new methods for directed mutagenesis would not be in line with obligations for regulatory oversight and risk assessment in accordance with the precautionary principle enshrined in European legislation.

Any previous decisions taken by authorities of EU member states which were based on other interpretations of the respective national biosafety legislation transposing Directive 2001/18/EC and thus not in line with the ECJ ruling were reviewed and repealed by the national CAs subsequent to publication of the ruling in July 2018.

Regarding other sectorial legislation, e.g. for seeds or food, a legal opinion by SPRANGER (2017) showed clearly that they do not contain provisions suitable for an evaluation of risks of nGM applications to human and animal health and to the environment comparable to the respective requirements implemented by the GMO regulatory framework. Seed legislation is focused on seed purity and during seed certification tests are carried out to evaluate the performance of the seed to be authorised. A risk assessment is not part of the authorisation process. The scope of food legislation does not cover cultivation of plants or breeding and feeding of animals. A risk assessment or authorisation before marketing is not foreseen for conventional food. In addition environmental effects are not covered at all by these two sectorial legislations. In the legal opinion by SPRANGER (2017) several other areas of legislation, e.g. plant protection products, feed, are described and analysed for their applicability for the assessment and regulation of nGM applications. However, SPRANGER (2017) concluded that none of these is adequate to reach the requirements regarding precaution and risk assessment with regard to human health or the environment as laid down in the EU legislation for GMOs.

3.1.3 **Risk assessment requirements for GMOs and nGM applications**

Risk assessment currently required for GMOs

The risk assessment requirements in the EU are laid down in several documents. The principles and detailed requirements are described in Directive 2001/18/EC, its Annexes, Regulation (EC) No 1829/2003, as well as in Regulation (EU) No 503/2013 and several guidance documents published by EFSA (EFSA 2010, EFSA 2011a).

The risk assessment is based on a case-by-case principle, meaning that every transformation event needs to be assessed separately. The assessment is guided by the intended use of the GMO (cultivation, food, feed, processing…), the introduced trait(s), the species of the transformed plant and its biology, as well as the receiving environment in case of cultivation.

According to EFSA (2010) and based on the principles laid down in Annex II of Directive 2001/18/EC the environmental risk assessment follows a stepwise approach including the following steps:

- problem formulation including hazard identification
- hazard characterization
- exposure characterization
- risk characterization
- risk management strategies
- overall risk evaluation

Based on the risk assessment requirements as laid down in Directive 2001/18/EC the EFSA Scientific Panel on Genetically Modified Organisms has defined seven areas of risk, which need to be evaluated according to these steps:

- persistence and invasiveness of the GM plant, or its compatible relatives, including plant-to-plant gene transfer,
- plant-to-micro-organism gene transfer,
- interaction of the GM plant with target organisms,
- interaction of the GM plant with non-target organisms, including criteria for selection of appropriate species and relevant functional groups for risk assessment,
- impact of the specific cultivation, management and harvesting techniques; including consideration of the production systems and the receiving environment(s),
- effects on biogeochemical processes,
- effects on human and animal health.

Risk assessment requirements for nGM applications

The general principles and the requirements laid down in the various guidance documents for the risk assessment of GMOs are applicable for nGM products, which meet the definition for GMOs according to Directive 2001/18/EC and are thus subject to the EU biosafety framework. Among others this concerns applications of e.g. cisgenesis/intragenesis, transgrafting, other products modified by rDNA methods (e.g. RNAi) and genome editing applications such as new mutagenesis techniques (including SDN-1, SDN-2, ODM) according to the ruling of the ECJ (ECJ 2018). For some types of nGM applications, cisgenesis/intragenesis, SDN-3, RNAi, opinions or documents by the EFSA GMO panel outlining respective assessment approaches are available (CASACUBERTA et al. 2015, EFSA-PANEL ON GMOS 2012a, EFSA-PANEL ON GMOS 2012b). Based on respective mandates by the European Commission EFSA is working on opinions on additional nGM applications, such as SDN-1 und SDN-2, which are scheduled to be delivered in late 2020.

Shortcomings identified in the current risk assessment approaches for GMOs are also relevant for the assessment of nGM products and will need to be addressed (AGAPITO-TENFEN et al. 2018), as will specifics associated with certain nGM approaches and products (ECKERSTORFER et al. 2019b, MODRZEJEWSKI et al. 2019).

3.1.4 Outstanding aspects of the existing EU regulatory framework

- EU legislation contains a dedicated (sectoral) regulatory framework for GMOs at the community level for environmental release and food and feed use, which was promulgated into legislation of member states.
- It outlines a complex distribution of regulatory responsibilities for risk assessment and decision-making between different EU-level and member states authorities and institutions.
- The framework mandates a comprehensive range of requirements (authorisation based on risk assessment, risk management and post-marketing environmental monitoring, coexistence measures for cultivation purposes, labelling requirements, submission of detection method, renewal of authorization after 10 years).
- The regulatory trigger is interpreted differently: it is mostly considered to be process-oriented (KRÄMER 2015, SPRANGER 2015), however another reading suggests that it relates to both process and product (KAHRMANN et al. 2017).
- Until late 2019 no policy decisions concerning nGM applications or any decisions concerning the regulatory status of individual nGM products were made at community level. No nGM product applications for unconfined environmental release or food and feed use are pending at the community level.
- Products regulated according to GMO legislation undergo a comprehensive risk assessment taking into account the characteristics of the modified organism, as well as the receiving environments in a case-specific manner to determine effects on health and environment (direct and indirect, immediate and delayed). Detailed guidance for assessment was developed and has to be applied.
- General agricultural, environmental or food and feed legislation applies for nGM-applications not covered by GMO legislation; however, the respective requirements have a different focus and do not achieve the same quality of assessment and level of protection as an assessment according to existing GMO regulations.

3.2 Norway

3.2.1 Main features of the Norwegian regulatory framework

Existing legislation

The Norwegian Gene Technology Act and the related Regulations for risk assessment (GTA 1993, GTA REGULATIONS 2005)[2] follow to a large extent the EU approach and the respective EU legislation. However, a main distinction is the requirement that the production and use of GMOs need to "take place in an ethically justifiable and socially acceptable manner, in accordance with the principle of sustainable development" (GTA 1993). This implies the requirement of a socio-economic assessment in addition to the assessment of risks to the environment and human health.

[2] http://bch.cbd.int/database/results?searchid=767235

Authorities involved in the authorisation process

The Competent Authorities are the Ministry of Climate and Environment (MOE) for deliberate release and placing on the market of GMOs, and the Ministry of Health and Care Services for contained use. The Norwegian Biotechnology Advisory Board is a scientific body appointed by the government, and responsible for delivering opinions on matters that are within the scope of the Gene Technology Act and other questions relating to biotechnology.

Regulatory approach

In Article 4 of the Norwegian Gene Technology Act a genetically modified organism is defined as: *"a microorganism, plant or animal in which the genetic material has been altered by means of gene or cell technology"*, while gene technology is defined as: *"techniques that involve the isolation, characterisation and modification of heritable material and its introduction into living cells or viruses"*. This means that the use of gene technology, as defined in the Gene Technology Act defines a GMO and therefore triggers the applicability of the Act.

The Norwegian Gene Technology Act foresees in its Article 10 that "Approval is not required for the placing on the market of a product that has been approved for placing on the market in another European Economic Area (EEA) state pursuant to the rules laid down in Annex XX, paragraph 25, of the EEA Agreement (Council Directive 2001/18/EEC)". However, the Norwegian authorities may prohibit or limit the placing on the market of such products, if they believe that involves a risk to health or the environment, or if placing on the market is otherwise in conflict with the purpose of the Gene Technology Act, meaning that also ethics, sustainability and social utility may constitute grounds for non-approval.

3.2.2 Coverage of nGMs by the Norwegian regulatory framework

According to information from the Norwegian Ministry of Environment (pers. comm.) most of the products derived from the application of nGMs may fall under the Gene Technology Act, unless it will be defined otherwise by the ministry or government and in consultation with the Biotechnology Advisory Board. However, as the Norwegian legislation is aligned with the EU legislation it will most likely follow a respective decision made on EU level.

The Norwegian Biotechnology Advisory Board (NBAB) has released a discussion paper regarding how organisms modified by nGM could be regulated (MOE pers. comm.)[3]. The discussion paper will be discussed in a series of open meetings with invited stakeholders organised by the NBAB. In this document a regulation of nGM applications on the basis of the degree of the genomic change is suggested, e.g. transient changes are proposed to be exempt from regulations and it is proposed that point mutations are subject only to notification with less rigorous assessment.

[3] http://www.bioteknologiradet.no/filarkiv/2010/07/genteknologiloven-engelsk-hele-for-web-v-2.pdf

3.2.3 Risk assessment requirements for GMOs and nGM applications

Risk assessment requirements for GMOs

The requirements for risk assessment are laid down in the "Regulation relating to impact assessment pursuant to the Gene Technology Act" and its Annexes[4]. These requirements are very similar to those defined in the EU by Directive 2001/18/EC.

However, in addition to risks to human health and the environment, the Norwegian legislation also foresees an evaluation of aspects related to socioeconomics, sustainability and ethics.

Risk assessment requirements for nGM applications

No specific requirements for the risk assessment of nGM applications have been discussed or introduced yet. If a specific nGM application is decided to be covered by the Gene Technology Act similar requirements as for other regulated GMOs would apply.

3.2.4 Outstanding aspects of the existing regulatory framework in Norway

- National GMO-law is harmonised with EU regulations, however it is including additional requirements for evaluation of effects on sustainability.
- Process-oriented regulatory trigger comparable to EU legislation, however wording referring more clearly to the biotechnological modification of heritable material.
- No decisions on the regulatory status of nGM applications were made ahead of the ECJ ruling, which will also influence policy decisions in Norway. However, most types of nGM applications, including applications of genome editing according to the ECJ ruling, would likely be covered by the Norwegian GMO legislation.
- Due to the mandatory assessment of effects on sustainability broader regulation scope as compared to EU framework requiring interdisciplinary approach.

3.3 Switzerland

3.3.1 Main features of the Swiss regulatory framework

Existing legislation

The Swiss regulatory framework for biotechnological applications in the non-human domain is closely aligned with the respective EU-legislation (SCNAT 2016). It consists of regulations on different political levels and is based on general principles contained in the Swiss constitution[5]. Among other considerations the precautionary principle shall be implemented to avoid harm or damages to the environment or human health and to minimise adverse effects by appropriate risk management measures. According to these principles a pre-authorisation risk assessment is required by the Swiss biosafety regulations.

[4] https://bch.cbd.int/database/record.shtml?documentid=10278

[5] https://www.bafu.admin.ch/bafu/en/home/topics/biotechnology/law/acts-ordinances.html

The main elements of the regulatory framework are the Federal Act on Non-Human Gene Technology (Gene Technology Act 2003, GTA[6]) and the Ordinance on the Handling of Organisms in the Environment (Release Ordinance 2008, RO[7]).

An overview of all relevant laws and regulations is presented by the Swiss Biosafety Clearing House[8].

Regulated activities comprise the work with GMOs under conditions of contained use, e.g. in research or industrial facilities, the deliberate release of GMOs into the environment, e.g. for field trials, or the placing on the market of GMOs for the application of GMOs in agriculture and environmental technology or for industrial purposes.

In 2005 a moratorium on placing on the market of GMOs for agricultural cultivation was introduced by a public referendum. In 2017 the Swiss parliament accepted the prolongation of the moratorium until 2021 and refused to implement a proposal by the involved authorities for the regulation for coexistence of non-GM and GM crops in agriculture.

Involved authorities

The main competent authority for regulation of GMOs is the Biotechnology Section of the Federal Office of the Environment (FOEN). According to the regulatory framework FOEN is responsible for

- the implementation of the Biodiversity Convention in the area of genetic resources
- the development and implementation of environmental regulations in the area of biotechnology and gene technology
- issues associated with the safe and sustainable use of biotechnology and gene technology, including the issue of bioethics
- all international activities in the area of environmental biosafety, in particular for the OECD and the Convention on Biodiversity (CBD)
- the development and implementation of the Environment Protection Law in the area of pathogens and non-native organisms

Depending on the intended use of the GMOs or GM products other federal authorities are involved in the respective authorisation procedures. Permits are only granted when all involved authorities are in favour of authorisation. Involved are

- the Federal Office of Public Health (FOPH) for food and biocidal products
- Swissmedic for products for medical use
- Federal Food Safety and Veterinary Office (FSVO) for immunobiological veterinary medicines

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[6] https://www.admin.ch/opc/en/classified-compilation/19996136/index.html (Note that the English translation of the GTA is provided for information purposes only and cannot be used as legally binding source text).

[7] https://www.admin.ch/opc/en/classified-compilation/20062651/index.html (again the English translation of the GTA is provided for information purposes only).

[8] http://www.sib.admin.ch/en/cartagena-protocol/laws-and-regulations/index.html

- the Federal Office for Agriculture (FOAG) for plant propagation material, animal feed, fertilisers or plant protection products

Regulatory approach

A general definition which organisms are considered as GMOs and thus regulated according to the GTA was included in the GTA[9]. This definition relates to genetic modifications, which are not due to naturally occurring processes. Further explanations which methods lead to modifications that generate GMOs and trigger regulatory action are provided in the RO[10]. According to the FOEN this regulatory trigger is considered process-oriented (Erass in SCNAT (2016).

However no final legal interpretation of this definition is available at present. Therefore the Swiss Federal Council decided that the regulatory status of all controversially debated applications needs to be clarified by the competent authority FOEN by means of case-by-case decisions (FOEN pers. comm.).

According to the precautionary principle regulated products need to undergo a mandatory risk assessment before authorisation is granted. This risk assessment is addressing the potential effects of the product in question on human and animal health as well as on the environment. The assessment needs to address intended as well as unintended effects and it needs to take into account that typically only incomplete knowledge is available on the effects of the introduced modifications (ECNH 2012).

In addition to the obligatory (environmental) risk assessment, the GTA requires a post-marketing environmental monitoring, the consideration of the right of consumers to freedom of choice (i.e. requiring measures for the protection of GMO-free production) and measures to prevent product fraud. In addition the GTA includes requirements to ensure public information and liability for effects which are caused by the use of authorised GM-products.

3.3.2 Coverage of nGMs by the Swiss regulatory framework

Switzerland has not yet adopted a definitive position on the regulatory status of individual nGM types or introduced specific legislation regulating products generated by nGMs. Currently applicants can submit formal requests to clarify the status of a specific application to the FOEN, which then decides on a case-by-case basis.

In current practice decisions are based on an interpretation of the definition of the GTA and the general requirements contained in the Swiss constitution, e.g. the precautionary principle. However no specific rules for implementation are provided in the constitution. A majority of members of the Swiss Ethics Committee on Non-Human Applications of GM-Technology (ECNH) concluded that these requirements and the currently limited knowledge on the intended and unintended effects of products generated by nGMs would require that a risk

[9] GTA Art. 5, Para 2: “Genetically modified organism means organisms in which the genetic material has been altered in a way that does not occur under natural conditions by crossing or natural recombination”.

[10] RO Art. 3, Sec (d): “genetically modified organisms means organisms in which the genetic material has been altered by methods of gene technology in accordance with Annex 1 (of the RO, addition), in a way that does not occur under natural conditions by crossing or natural recombination …”

assessment is conducted for such applications similarly as for GM plants subject to the GTA (ECNH 2016). Therefore the current policy of the FOEN is to enforce the requirements of the GTA per default in a similar way as for GM plants (FOEN pers. comm.).

In addition a national debate involving a broad range of stakeholders was initiated in 2017 to address the question whether or how nGM applications should be regulated and/or assessed in the future. The stakeholder discussion focused on several examples of nGM-applications, e.g. herbicide resistant oilseed rape developed by ODM, wheat with resistance to powdery mildew developed by genome editing (CRISPR-Cas), wheat with lowered gluten-content also developed by genome editing (CRISPR-Cas) and apple varieties developed by accelerated breeding involving intermediate transgenic plant generations. In addition hornless dairy cows developed by genome editing (specifically by modification using a Transcription Activator-Like Nuclease (TALEN) system) and the application of RNA-based insecticides (which kill Varroa-mites via RNAi induced silencing of essential mite genes) were discussed (FOEN pers. comm.). However none of these applications nor any other nGM applications are presently submitted for authorisation in Switzerland.

It was noted that the RO would need to be adapted to specifically address nGM applications like genome editing which lead to similar modifications as classical mutagenesis if a political consensus would emerge to exempt such applications; the shift to an entirely product-based regulatory system would require an extensive amendment of the current legal framework (SCNAT 2016).

nGM applications are subject to the general regulations for agricultural products, particularly the Ordinance on Production and Marketing of Plant Propagation Material (Seeds Ordinance). However these regulations contain no requirements for the environmental risk assessment and the safety assessment of new traits which are comparable to the assessments conducted for GMOs. Furthermore no labelling is required according to these regulations. Regulations for prevention of environmental impact due to release of invasive species are under discussions (FOEN pers. comm.).

3.3.3 Risk assessment requirements for GMOs and nGM applications

Risk assessment requirements for GMOs

The requirements for risk assessment of GMOs are laid down in the RO (Article 7)[11]. These requirements are very similar to those defined in the EU by Directive 2001/18/EC.

[11] (a) the health of human beings and animals cannot be endangered, in particular by toxic or allergenic substances or through the spread of antibiotic resistances;

(b) the genetically modified organisms cannot spread or multiply in an uncontrolled way in the environment;

(c) no undesired properties can be permanently passed on to other organisms;

(d) populations of protected organisms, in particular those included in the Red Lists, or organisms that are important for the ecosystem in question, in particular those that are important for the growth and reproduction of plants, are not affected;

(e) no species of non-target organisms can be endangered;

(f) the material balance of the environment is not severely or permanently impaired;

Environmental monitoring is conducted in the framework of risk management with a view to the potential impacts of a particular GM product.

Risk assessment requirements for nGM applications

Switzerland is currently debating biosafety issues related to nGMs in the context of the relevance and applicability of the existing national GMO legal framework. Swiss authorities are looking into the possible need for adjustment of the existing legal framework, with regard to biosafety, potential adverse effects on biological diversity, food security, human health and consumer choice.

ECNH suggested that an adequate risk assessment which takes into account that typically only incomplete knowledge on the effects of modifications introduced by nGMs is available. Accordingly unintended and unexpected effects associated with nGM applications – like GMOs - should be assessed according to a probabilistic approach rather than with a causal assessment model. The assessment should be based on the new product in its entirety instead of focusing on aspects of the new traits only (ECNH 2016).

Similar as for GMOs associated environmental effects should be addressed by appropriate environmental monitoring (FOEN pers. comm.).

3.3.4 Outstanding aspects of the existing regulatory framework in Switzerland

- The Swiss Gene Technology Act is closely aligned with the EU regulatory framework and includes similar requirements. At present a moratorium for unconfined environmental releases and marketing of GMOs is in place until 2021.
- A precautionary approach would also be required for biotechnological applications not covered by the GTA according to constitutional requirements. However no specific administrative regulations are available for the implementation of this principle.
- Currently no general legal interpretation of the process-oriented regulatory trigger by the government is available. Therefore the respective authorities need to decide in interpretation of the existing legislation if nGM applications are submitted.
- An ongoing national discussion process involving authorities and national stakeholders is addressing specific regulatory issues for a range of case studies concerning different nGMs (including genome editing for plants and animals).
- Field trials with nGM plants are conducted under confined conditions (using a so called “protected site” surrounded by fencing to avoid public access and/or vandalism).

(g) important functions of the ecosystem in question, in particular the fertility of the soil, are not severely or permanently impaired;

(h) in experimental releases, none of the new properties based on genetic modification can be permanently passed on to wild flora or fauna.

3.4 USA

3.4.1 Main features of the US regulatory framework

Existing legislation

The regulatory approach towards GMOs and GM-products as implemented in the USA is laid down in the Coordinated Framework (CF) for the Regulation of Biotechnology, which was established in 1986 by the White House Office of Science and Technology Policy (OSTP) and updated in 1992 and again in 2017 (NAS 2016, EOP 2017). The CF presents a comprehensive outline of the US regulatory policy addressing the safety of the full range of biotechnological products, including plants, animals and microorganisms. The CF did not introduce new legislation and additional statutory rights of a single agency, but rather relied on an existing framework of laws addressing different regulatory matters. These laws are not specifically focused on GMOs or GM-products, but were initially developed to regulate non-GM products with a view to application of these products in medicine, agriculture and environmental protection. Among others these laws regulate foods, drugs or pesticides, or organisms which are considered to have a potential to act e.g. as a plant pest. The respective regulations therefore address issues relevant for the safety of biotechnological products.

The laws implicated in the CF include the following:

- The Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA)[12].
- The Toxic Substances Control Act (TSCA)[13].
- The Federal Food, Drug, and Cosmetic (FD&C) Act[14.]
- The Plant Protection Act (PPA)[15]
- The Animal Health Protection Act (AHPA)[16]

In addition other legislation pertaining to the oversight and safety of food, veterinary and other biological products are included in the CF (EOP 2017).

The statutes of these existing laws were considered adequate to also regulate products developed by biotechnology, including GMOs, for similar intended scopes of use as non-GM products with comparable characteristics (NAS 2016).

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[12] 7 U.S.C. §136 et seq. (1996): https://www.gpo.gov/fdsys/pkg/USCODE-1996-title7/pdf/USCODE-1996-title7-chap6.pdf

[13] 15 U.S.C. §2601 et seq. (1976) as amended by the Frank R. Lautenberg Chemical Safety for the 21st Century Act https://www.gpo.gov/fdsys/pkg/USCODE-2016-title15/pdf/USCODE-2016-title15-chap53.pdf

[14] 21 U.S.C. Ch. 9, §301 et seq. (1938) https://www.gpo.gov/fdsys/pkg/USCODE-2016-title21/pdf/USCODE-2016-title21-chap9.pdf

[15] 7 U.S.C. Ch. 104, §7701 et seq. (2000) https://www.gpo.gov/fdsys/pkg/USCODE-2000-title7/pdf/USCODE-2000-title7-chap104.pdf

[16] 7 U.S.C. Ch. 109, §8301 et seq. (2002) https://www.gpo.gov/fdsys/pkg/USCODE-2002-title7/pdf/USCODE-2002-title7-chap109.pdf

Further guidance for the implementation of the CF by the responsible agencies was established in 1992 and in 2017 with respective updates to the Coordinated Framework for the Regulation of Biotechnology (EOP 1992, EOP 2017).

Involved authorities

The main responsibilities for implementation of the CF are divided between three US agencies which have statutory rights according to the above mentioned laws (NAS 2016). Under the CF no lead regulator is appointed, all involved agencies are cooperating as equivalent partners according to their specific statutory remits.

Whether a biotechnology product is regulated by all three agencies or specific agencies only depends on the characteristics of the product (e.g. plant pest or noxious weed) and its intended uses (e.g. products for food and feed use, or plant-incorporated protectants):

- The Animal and Plant Health Inspection Service (APHIS), an agency of the USDA, is responsible for implementation of the Plant Protection Act and the Animal Health Protection Act. Concerning plants generated by biotechnology APHIS regulates importation, interstate movement, and the environmental release of plants, which may exhibit plant-pest characteristics and/or is known to be a noxious weed (WOLT et al. 2016).
- The U.S. Environmental Protection Agency (US-EPA) is the responsible authority according to the FIFRA and the TSCA. Regarding GMOs US-EPA is concerned with the environmental release and placing on the market of GMOs with plant-incorporated protectants and genetically modified microbial pesticides, e.g. modified Bt-toxins (SPRINK et al. 2016b). US-EPA oversight is aimed to prevent that such products pose unreasonable risks to human health and the environment according to the standards set under section 408 of the FD&C Act (EOP 2017).
- The U.S. Food and Drug Administration (FDA), an agency of the Department of Health and Human Services Authorization is responsible for implementation of the Federal Food, Drug, and Cosmetic Act, in particular as food and feed safety and the safety of biotechnological products for medical use are concerned (CAMACHO et al. 2014, SPRINK et al. 2016b).

The three mentioned agencies have developed a number of agency-specific regulations, rules, and policy documents for implementation of their responsibilities and updated them as necessary since the CF was introduced. References to these documents are included in the recent update of the CF (EOP 2017).

Oversight by USDA/APHIS

USDA/APHIS provides regulatory oversight for the environmental release of GMOs, e.g. field trials of regulated GMOs for agricultural applications and the unconfined use of GM plants which were determined to exhibit plant pest characteristics or which produce a pharmaceutical compound. A description of this regulatory process is provided by Title 7, part 340 of the Code of Federal Regulations (CFR). Different avenues for regulation exist for different scopes of release applications:

- Permit requests and notifications for import, interstate movement, and environmental release for field testing of regulated GM crops.

Applications for permits (for plants and other organisms) need to be approved by APHIS based on confinement and appropriate risk management measures; a more streamlined procedure for applications is possible for multiple subsequent releases of specific GM plants, which are considered to be of lower risk.

- According to the Plant Protection Act of 2000 and Title 7 CFR part 340.6 APHIS can approve petitions for deregulated status based on the results of a plant pest risk assessment (PPRA) conducted by APHIS. An environmental assessment (EA) or an environmental impact statement (EIS), which informs the agency about the environmental impacts, if any, of the decision, may also be conducted. Such a deregulation is necessary for the unconfined release of GM plants, like for (commercial) use in agriculture.

Oversight by US-EPA

The regulatory authority of EPA towards GM crops according to FIFRA is limited to traits developed to intentionally exhibit pesticide activity. Accordingly regulatory oversight and risk assessment by EPA is focused on the pesticidal properties of regulated items rather than the crop itself (WOLT et al. 2016).

Oversight by FDA

Oversight by FDA according to the FD&C Act is aimed to ensure that foods and feeds derived from GMOs are as safe as their non-GM counterparts. The FDA evaluates the safety of foods and feeds derived from GM crops with a focus on the compositional equivalence of the GM product and its non-GM comparator, especially as the occurrence of allergens, anti-nutrients and toxins in the biotechnological product is concerned (WOLT et al. 2016). FDA decided that GM foods from new plant varieties have “generally recognized as safe” (GRAS) status and do not require an approval by FDA unless determined to be a food additive regulated according to the FD&C Act. Since 2001 FDA, however, implements a premarket consultation procedure to confirm this status for individual GM food and feed products.

Regulatory approach

The US system for regulation of biotechnology products is not relying on a specific definition of regulated products which is used by all involved statutory agencies. Instead regulatory oversight is triggered by specific characteristics of the product in question which implies that a higher risk is posed to the environment and/or human and animal health than exhibited by other products under conditions of similar use. The determination whether an organism will be regulated is based on whether the particular organism is a plant pest or has been engineered using a plant pest according to the propositions in the mentioned regulations.

Therefore regulation of GM plants in the USA is not triggered by the genetic modification of organisms with recombinant DNA (rDNA) techniques themselves, or by the “novelty” of the products, but by specific product characteristics as defined in the different pieces of relevant legislation:

- USDA-APHIS is regulating GM plants, which may exhibit plant-pest characteristics and/or are known to be a noxious weed. A description of the products regulated by APHIS is included in Title 7 CFR, part 340[17].
- Regulation by US-EPA is triggered by pesticidal properties or environmental toxicity of a specific GM product.
- A food safety evaluation is conducted for specific GM foods and feeds with adverse allergenic, toxicological or nutritive properties due to substantial compositional differences compared with other products, which have already been granted GRAS status. However at present the GRAS status of GM products is usually confirmed by the developers by voluntary consultation with the FDA.

In summary the US regulatory framework and particularly its implementation concerning GM plants by APHIS is based on product-specific characteristics as regulatory trigger. These characteristics may include e.g. a higher risk of becoming a plant pest than comparable conventional crops, exhibit unreasonable environmental impacts or pose risks for human and animal health by a changed composition or as an effect of the traits which are intentionally or unintentionally expressed due to the genetic modifications induced (NAS 2016).

However, as recognized by NAS (2016) some aspects of the approach need to be reviewed for consistency as crops developed by *Agrobacterium tumefaciens* mediated transformation are considered to be regulated irrespective of the plant pest potential of the engineered traits, whereas comparable GM crops developed by other methods, e.g. biolistic transformation, are not automatically regulated.

3.4.2 **Coverage of nGMs by the US regulatory framework**

In recent years a number of nGM plants have been reviewed by APHIS whether they would be subject to regulation according to Title 7 CFR, part 340 (plant pest potential) or Title 7 CFR, part 360 (as noxious weeds) (CAMACHO et al. 2014, NAS 2016, WALTZ 2018, WOLT et al. 2016, WOLT&WOLF 2018).

These decisions are made upon request for individual nGM applications, i.e. specific nGM plants. Similar challenges as noted above for GM plants are encountered regarding the determination of the plant pest potential of the application to trigger regulatory oversight. Determination of the regulatory status is based on the origin of the genetic material and the vector used in the development of the nGM plant. If either involves a plant pest, then the nGM plant is regulated, otherwise nGM plants are not regulated by APHIS.

[17] Any organism which has been altered or produced through genetic engineering, if the donor organism, recipient organism, or vector or vector agent belongs to any genera or taxa designated in §340.2 and meets the definition of a plant pest, or is an unclassified organism and/or an organism whose classification is unknown, or any product which contains such an organism, or any other organism or product altered or produced through genetic engineering which the Administrator determines is a plant pest or has reason to believe is a plant pest. Excluded are recipient microorganisms which are not plant pests and which have resulted from the addition of genetic material from a donor organism where the material is well characterized and contains only noncoding regulatory regions.

Between 2011 and August 2019 a variety of GM/nGM plants developed with transformation methods other than Agrobacterium mediated transformation and/or constructs containing genetic elements derived from species which are known to exhibit plant pest characteristics were assessed for their regulatory status. In that timespan some 40 inquiries were submitted regarding the regulatory status of different nGM applications. In 2018 and 2019 all but two of these inquiries were for genome edited plants, the rest being applications of cisgenesis and intragenesis. Only one nGM application (a cisgenic scab-resistant Apple) was determined to be regulated by APHIS because genetic material from a plant pest was retained in the organism[18]. All others were determined not to meet the definition of a regulated article.

The total requests concerned a variety of different nGMs: e.g. many genome editing applications including ZFN, MN and more often TALEN applications as well as an ever inceasing number of applications of CRISPR-mediated genome editing (mostly SDN-1 genome editing-applications), 6 requests regarding cisgenic/intragenic plants (or offspring from cisgenic plants) and several null-segregants (developed for nGM approaches such as epigenetic engineering, accelerated breeding and chromosome elimination purposes). The requests concerned method development as well as applications directed to development of a variety of traits (disease-resistance, compositional modification, drought and salt tolerance and modified developmental characteristics such as delayed flowering). The nGM applications were implemented for development of major crops (including maize, wheat, soybean, rice and potato) as well as for tobacco, alfalfa, pennycress, camelina and wild foxtail millet and some for perennial plants like apple and plum trees.

An amendment to the existing regulations, which would have included criteria for designating GMO which fall under the regulations as well as a revised procedure to determine whether regulated GMOs would pose risks as plant pests or noxious weeds was recently withdrawn (FEDERAL REGISTER 2017). These draft regulations recommended that some nGM applications (complete null-segregants derived from GMOs, nGMs like genome editing applications which induce targeted sequence changes like base substitutions or deletions (i.e. SDN-1 and SDN-2 applications) and nGMs, which are only introducing naturally occurring sequences from sexually compatible relatives, like cisgenesis applications) should be exempted from regulation. An additional round of consultation is scheduled to re-engage with stakeholders to determine the most effective, science-based approach for regulating the products of modern biotechnology (FEDERAL REGISTER 2017).

Meanwhile USDA confirmed that it will continue to grant non-regulated status to plants produced by the above mentioned techniques, e.g. plants developed by genome-editing techniques, including CRISPR-Cas9 under the following circumstances[19]:

The changes in these plants could also have been created using mutation breeding techniques (e.g. deletions of any size, single base-pair substitutions, insertions of nucleic acid sequences derived from sexually compatible plant relatives, complete absence of any prior introduced transgenic sequences, as e.g. in null-segregants).

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[18] https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated/regulated_article_letters_of_inquiry/regulated_article_letters_of_inquiry

[19] Details on USDA Plant Breeding Innovations (28.3.2018): https://www.aphis.usda.gov/aphis/ourfocus/biotechnology/brs-news-and-information/pbi-details

The plants are developed without the use of a plant pest as the donor or vector and they are not themselves plant pests.

In response to an increasingly confusing patchwork of labelling requirements by different US states, the USDA developed a National Bioengineered Food Disclosure Standard (NBFDS). which was enacted on December 21 of 2018 and shall be implemented in the time period from January 2020 until January 2022[20]. The labeling requirement is only mandatory for foods, it is relating in particular to the three topmost important ingredients and is introduced with a 5% threshold for the inadvertent presence of bioengineered material per ingredient. It was unclear, whether food produced from gene-edited plants will need to be labelled as such[21]. However the labelling requirement is not introduced for foods where modified genetic material is not detectable.

3.4.3 **Risk assessment requirements for GMOs and nGM applications**

Once the regulatory status of a plant developed by either GM methods or nGMs is determined by the respective regulatory agencies, similar requirements as for any other regulated items apply with regards to risk assessment. Specific risk assessment approaches are implemented by the different regulatory agencies involved in the CF for any application falling under their respective authority. If one of the agencies, e.g. APHIS, determines that a specific GM- or nGM application is not subject to regulation, e.g. according to Title 7 CFR, part 340, assessment of such applications may still be required by the other agencies.

The information required for the plant pest risk assessment conducted by APHIS is outlined by Title 7 CFR part 340.6, including e.g.

- information to assess, whether the GMO is more invasive or weedy,
- information, whether it is more susceptible to pests or diseases,
- information, whether the regulated plant results in adverse effects on non-target organisms,
- information, whether adverse effects due to gene flow to wild relatives and other organisms occur.

Environmental assessments (EAs) or environmental impact statements (EIS) for GM plants with pesticidal properties prepared under the Environmental Policy Act are taking into account the information requirements mandated by EPA for pesticide registration (NAS 2016). Information and guidance for implementation is available from EPA[22].

The food safety is the responsibility of the developer, however in practice FDA is routinely consulted by developers on the assessment of food safety of new substances which are intentionally or unintentionally present in the products derived from GMOs until all questions

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[20] USDA, Agricultural Marketing Service 7 CFR Part 66, Docket No. AMS–TM–17–0050. National Bioengineered Food Disclosure Standard, https://www.govinfo.gov/content/pkg/FR-2018-12-21/pdf/2018-27283.pdf

[21] Nature, The week in science: CRISPR crops, Nature 556, 10 (2018), doi: 10.1038/d41586-018-03913-y

[22] https://www.epa.gov/regulation-biotechnology-under-tsca-and-fifra

put forward by FDA have been resolved (NAS 2016). Guidance by FDA concerning the process and the assessment approach is available[23]. According to reports the developers of nGM crops, like false flax with modified oil composition which was created by SDN-1 CRISPR-Cas9 technology, will present the product to FDA for a voluntary review, even if the product determined to be not regulated by APHIS (WALTZ 2018).

In addition to the biotech evaluation other general requirements as for any plant or plant material need to be observed, like the Plant Protection and Quarantine (PPQ), permit and/or quarantine requirements implemented by APHIS. Such requirements may still apply for biotech plants which are not regulated according to the current requirements of the CF or which may be excluded from biotech regulation by a future revision of the existing legislation.

3.4.4 Outstanding aspects of the existing regulatory framework in the USA

- A coordinated framework for the regulation of biotechnology applications was introduced in 1986 based on existing legislation and statutory authorities (USDA-APHIS, US-EPA, FDA).
- The CF was revised in 1992 and 2017, with a focus on GM applications; a proposal for further revision with a view to nGM applications (including genome editing, cisgenesis, use of null-segregants) is under discussion.
- The elements of the CF use product-oriented regulatory triggers addressing a range of risk-issues (plant pathogenicity, weediness, adverse effects of pesticidal applications and food safety). However some triggers (plant pathogenicity) are implemented in a method-oriented way.
- USDA-APHIS and EPA review individual products for their regulation status; a broad range of GM plants regulated by other national frameworks was considered not-regulated by APHIS. Similarly a growing number of nGM applications has been granted non-regulated status by APHIS in the recent years.
- Risk assessment requirements for regulated products are determined in a case-specific approach; like in other frameworks these risk assessment requirements are more comprehensive as compared with requirements for non-regulated products.

3.5 Canada

3.5.1 Main features of the Canadian regulatory framework

Existing legislation

While the first field trials for GM-plants in the 1980ies and early 1990ies were regulated by available existing legislation, i.e. under the Seeds Act (1985), the Feeds Act (1983), and the Food and Drugs Act (1985); the federal government of Canada introduced a new policy addressing plants with novel traits (PNT), as well as novel foods and feeds in 1993. This new

[23] Guidance for Industry: Recommendations for the Early Food Safety Evaluation of New Non-Pesticidal Proteins Produced by New Plant Varieties Intended for Food Use: https://www.fda.gov/Food/GuidanceRegulation/GuidanceDocumentsRegulatoryInformation/ucm096156.htm

"Regulatory Framework for Biotechnology" was not based on entirely new laws or regulating authorities, but rather on existing legislation and regulatory bodies to regulate biotechnology products. Therefore the regulatory framework for novel biotechnology products implements similar general principles and regulatory structures as implemented for non-GM products for comparable purposes, including agricultural use. However the concerned legislation was amended according to the new policy and some new implementing regulations were established to address specific regulatory aspects and administrative procedures for novel biotechnological products.

For different kinds of biotechnological products different legislation as well as authorities, which are responsible for the respective regulatory processes and products are relevant[24]. Novel agricultural products are subject to the following laws and regulations:

- The Seeds Act and the Seeds Regulation are relevant for plants, including plants with novel traits and trees. The responsible agency is the Canadian Food Inspection Agency (CFIA).
- The Feeds Act and the respective Feeds Regulations regulate feeds, including novel feeds. The CFIA is responsible for its implementation.
- The Health of Animals Act and the respective Health of Animals Regulations are relevant for Veterinary Biologics and are implemented by the CFIA.
- The Fertilizers Act and the respective Fertilizers Regulations regulate fertilizer supplements, (microbial and chemical). The responsible authority is the CFIA.
- The Food and Drugs Act and the Food and Drug Regulations (Novel Foods Regulation), the Medical Devices Regulations, and the Cosmetics Regulations are relevant for foods, drugs (human and veterinary), cosmetics, and medical devices. The responsible authority is Health Canada (HC).
- Pest Control Products Act and the Pest Control Products Regulations regulate pest control products and are implemented by the Pest Management Regulatory Agency and HC.
- Canadian Environmental Protection Act and the linked New Substances Notification Regulations (Organisms) are relevant for fish products and all other animate products of biotechnology not covered under other federal legislation. The responsible authorities are Environment Canada and HC (in cooperation with Fisheries and Oceans Canada).

Access to the legal texts mentioned above is provided by CFIA[25].

In 1999 the Canadian Environmental Protection Act (CEPA) was introduced to establish regulatory oversight by Environment Canada for any products or end-uses which were not regulated by other acts (SHEARER 2014).

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[24] http://www.inspection.gc.ca/plants/plants-with-novel-traits/general-public/overview/eng/1338187581090/1338188593891

[25] List of Acts and Regulations: http://inspection.gc.ca/about-the-cfia/acts-and-regulations/list-of-acts-and-regulations/eng/1419029096537/1419029097256

Involved authorities

Several agencies are involved in the regulation of agricultural products. The main regulators are the Canadian Food Inspection Agency (CFIA), Health Canada (HC) and Environment Canada as indicated above.

For the regulation of agricultural applications, in particular PNTs and novel foods CFIA and HC are responsible for different aspects:

- The Canadian Food Inspection Agency (CFIA) is the leading authority for agricultural products of biotechnology and responsible for regulation of the environmental release of PNTs as well as for feeds derived from PNTs and for the environmental risk assessment of new crops. Authorisation by CFIA must be obtained prior to conducting confined field trials or unconfined releases, i.e. for commercialization (NAS 2016).
  CFIA is regulating the performance and the environmental safety of the respective products as well as for inspection and monitoring after approval of products (including imported biotechnology products).
- Health Canada has primary responsibility according to the Food and Drugs Act for consumer health related issues and the setting of standards for the safety of (novel) foods.

With regard to labelling of products the responsibility of both authorities is shared: The CFIA is responsible for non-safety related, voluntary product labelling and consumer fraud issues, while Health Canada is responsible for required labelling related to health and safety issues addressing e.g. allergenicity and changes in nutritional composition. However there is no mandatory labelling of novel seeds or foods which is comparable to the GM-labelling regime in the EU.

Regulatory approach

According to CFIA[26] Canada implements a product-oriented rather than a process-oriented approach to triggering regulatory oversight for all products of biotechnology, including PNTs. The trigger for regulation in all cases is based on the “novelty” of the product, e.g. the traits exhibited by a specific plant, rather than on the method used to introduce the novel traits. A similar approach is used for the regulation of novel foods and feeds, novel aquatic organisms and new substances[27].

A trait is considered to be novel when it displays both of the following characteristics:

- it is “novel”, i.e. not present in stable, cultivated populations of the respective plant species in Canada, or if the expression of existing traits is modified to levels, which are significantly outside the range established by cultivated varieties and
- it has a potential to result in adverse environmental effects.

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[26] "Novelty" and Plants with Novel Traits: http://www.inspection.gc.ca/plants/plants-with-novel-traits/general-public/novelty/eng/1338181110010/1338181243773

[27] Novel Foods, Including Novel Foods that are Products of Genetic Modification: http://www.inspection.gc.ca/food/labelling/food-labelling-for-industry/method-of-production-claims/eng/1389379565794/1389380926083?chap=3

The determination of the novelty status of a new plant variety according to Part V of the Seeds Regulation is primarily the responsibility of the developer and decided upon by the Plant Biosafety Office (PBO) of CFIA on a case-by-case basis based upon specific guidelines issued by CFIA (CFIA 2009).

PBO is also responsible for establishing and implementing policy for PNTs as well as for decisions to authorise specific PNTs. In all of these aspects the Biotechnology Risk Assessment Unit (PBRA) at CFIA is providing scientific support to the PBO (SHEARER 2014).

The broad regulatory approach implemented with the novelty concept in Canada includes plants whose novel traits were introduced by conventional breeding or use of nGMs, including e.g. herbicide resistant crops developed by conventional breeding approaches including mutation breeding or any nGM. However these crops currently constitute only a minority of the authorised applications as compared to the number of GM crops notified for authorisation.

The Canadian system is sometimes considered to be less predictable and certainly requires more expenditures, e.g. by the regulators, than systems which implement a strictly process-oriented definition to trigger regulatory action. However discussions between the regulators and the developers for the determination of the regulatory status were only necessary for a minority of applications (approx. 5%), in most cases due to the "novelty" criterion. The question whether risks may be associated with an application was less of an issue, as regulators consider plausibility of potential effects as sufficient for their decision (CFIA pers. comm.).

Since the determination of the regulatory status is sometimes challenging the developers are invited to consult with the authority (NAS 2016). Such pre-submission consultation (meetings) with all involved authorities are possible for developers who wish to discuss the "novelty" status of the product in question and clarify the content of the submission, particularly specific information requirements for risk assessment. Specific guidance for pre-submission consultation was developed by Health Canada and the CFIA (SHEARER 2014).

It needs to be noted, that the specific wording of the regulatory trigger is not identical for novel foods, novel feeds, and PNTs (SHEARER 2014)[28].

Differences are caused by e.g. exemptions of certain plants from PNT status, particularly due to a history of safe use prior to 1993. According to the seeds regulation (Sec. 108-3) three reasons exist why certain products may be exempted: Seeds already grown before 1996, and seeds derived from and/or substantially equivalent to seed grown before 1996 are not regarded as PNTs. Also plants grown in containment facilities (e.g. research with such plants conducted in greenhouses) are not subject to the requirements according to the PNT regulations.

Examples of products exempted from being assessed as a PNT include triticale (released in Canada in 1969), and triazine-tolerant canola (displaying novel herbicide tolerance) (SHEARER 2014).

[28] The specific definition of "novel foods" is provided in the Food and Drug Regulations (C.R.C., c. 870), the definition of "novel traits" according to the Feed Regulations is contained therein (Feed Regulations SOR/83-593).

However, food or feed products derived from plants which are not regulated as PNTs under the Seeds Regulations for the above reasons would not necessarily be exempted under the Food and Drugs or Feeds Regulations as novel foods and novel feeds. Therefore requirements for risk assessment for food and feed safety can still apply for such products.

As reviewed by NAS (2016) all GM plants have been considered to contain novel traits and have been assessed for environmental safety. This however might change in the future, e.g. for plants developed by re-transformation or re-mutation, which contain only traits that have already been reviewed for safety in the framework of previous applications. Such applications would still be subject to the PNT regulations, however a full risk assessment would not be required and the authorization for environmental release of such plants could be greatly simplified (SHEARER 2014).

Different regulatory requirements can also be caused by specific scopes of use. Specific applications, e.g. PNTs like herbicide resistant grass plants, which are not intended to be used as foods would not trigger all involved regulations. In that case an authorisation for use as novel food would not be necessary. On the other hand produce from virus-resistant citrus plants which cannot be cultivated in Canada for biological reasons may not require authorisation for environmental release, but would still be regulated as a novel food (SHEARER 2014).

As mentioned above no mandatory GM- (or rather PNT-) labelling is required. Also no general monitoring requirements are implemented. However conditions for authorisation of some products required the implementation of specific stewardship measures, like measures for management of resistance to Bt-toxins in target insects or herbicide resistance in weeds. Such stewardship measures and risk management measures for confined releases are subject to inspection by CFIA (CFIA pers. comm.).

3.5.2 **Coverage of nGMs by the Canadian regulatory framework**

The Canadian system regulates novel crops irrespective of the methods used to generate them, i.e. GM-methods, application of nGMs or conventional breeding approaches may lead to PNTs if they give rise to “novel” traits which are not present in cultivars of the same species grown in Canada or if the expression of existing traits is modified to levels which are significantly outside the range established by cultivated varieties (NAS 2016).

It is considered a purely product-oriented approach and is therefore presenting no challenges to accommodate crops developed by application of nGMs (SCHUTTELAAR 2015). The particular nGM crops, which are subject to the PNT regulations, are determined in a case-by-case approach by the regulators.

Information on the regulatory status is only disclosed for nGM applications, which are determined to result in PNTs and are further regulated according to the PNT requirements (SCHUTTELAAR 2015). As reviewed by SMYTH (2017) a number of different nGM crops were regulated according to the PNT regulations and risk assessed by CFIA. Between 2012 and 2016 12 crop varieties developed by different nGMs were approved, mostly maize, soy and canola varieties (SMYTH 2017). In addition the study addressed the CFIA regulatory process for an RNAi-application in apples (Arctic Apple™ by Okanagan Speciality Fruits) and a potato developed by cisgenesis/intragenesis (Innate™ by Simplot). In conclusion the PNT

regulations are considered to be fit for the purpose to appropriately regulate nGM plants (SMYTH 2017).

nGM applications, which do not result in PNTs, are only subject to general requirements which apply for all agricultural crops according to the Canadian legislation (SCHUTTELAAR 2015). In this respect Canada requires oversight on some crops in the framework of variety registration. The respective requirements mostly concern issues like quality, maturity and seed characteristics. For some crops that are known for the production of harmful substances (e.g. potato) additional requirements apply. Other crops, like corn, do not need variety registration. The assessment approach is different compared to the environmental risk assessment conducted according to the PNT regulations (CFIA pers. comm.).

3.5.3 **Risk assessment requirements for GMOs and nGM applications**

Once the regulatory status of an nGM application is determined to meet the PNT definition, similar requirements as for any other PNT (including GM-plants) apply regarding risk assessment.

The objective of the Canadian risk assessment requirements according to the PNT regulations is to ensure the protection of human and animal health and the environment (CFIA 2008). Additionally the Canadian framework aims to ensure consumers health and to protect consumers against fraud. The regulations should also ensure that international quality and safety standards to facilitate trade are maintained.

Before any novel products are registered, licensed or may be used commercially, regulators must determine:

- the potential effect of the product on human and/or animal health;
- the potential environmental impact of the product; and
- the merit or efficacy of the product (on some agricultural products)

Socio-economic considerations, e.g. regarding respective benefits of novel products, are not addressed by the required evaluation.

Applicants have to submit relevant information on the description of PNTs and their modification as well as on their biology and interactions with the environment as the basis for a safety assessment. Based on the intended scope of use of a PNT an environmental assessment and/or a livestock feed assessment of the PNT is then carried out by different branches of CFIA. The two types of assessment are complementary to each other and some of the information used for the respective assessments is overlapping (e.g. description of the novel traits and genetic modification(s) introduced).

For the environmental safety assessment of PNTs CFIA applies the following five criteria according to CFIA's Directive 94-08 (Dir94-08) (CFIA 2008):

- potential of the PNT to become a weed in agriculture or be invasive in natural habitats
- potential for gene flow to sexually compatible plants whose hybrid offspring may become more weedy or more invasive
- potential for the PNT to become a plant pest

- potential impact of the PNT or its gene products on non-target species, including humans
- potential impact on biodiversity

To address the above mentioned issues Dir94-08 includes the following information requirements (CFIA 2008)[29]:

- the identity and the origin of the PNT
- the properties of the novel gene and gene products
- the relative phenotypic expression of the PNT compared to a similar counterpart, if respective differences are anticipated
- anticipated or known relative effects in the environment resulting from the release

In addition CFIA prepared guidance for the assessment of novel feeds informing the required feed safety assessment[30].

The food safety assessment for novel foods derived from genetically modified plants, which is conducted by HC is based on the approach developed by the Codex Alimentarius Commission to assess the safety of foods derived from recombinant-DNA plants (CODEX ALIMENTARIUS COMMISSION 2003). Based on the Codex Guidance HC developed its "Guidelines for the Safety Assessment of Novel Foods"[31]. These guidelines outline the requirements for risk assessments and the criteria considered during assessments of the safety to human health from genetically modified microorganisms and plants.

Part of the decision whether a particular new crop is considered a PNT is based on the potential of the particular crop to result in adverse effects. Thus a pre-evaluation of possible risks is therefore conducted by the applicant and the respective conclusions need to be accepted by the regulating authority, i.e. the CFIA (NAS 2016). This pre-evaluation, however, is conducted without access to the results of a full risk assessment, which is only prepared after the PNT status is confirmed.

3.5.4 Outstanding aspects of the existing regulatory framework in Canada

- Existing regulations for plants, animals, microorganisms and food were updated to address "novel" products developed e.g. with biotechnology and are implemented by the statutory authorities responsible for the legislation in the respective areas.
- The regulatory trigger is a combination of novelty and plausibility for risks (for the risk issues covered in risk assessment of regulated products).

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[29] Data Required for Safety Assessments of Plants With Novel Traits and/or Novel Livestock Feed Derived From Plants: http://www.inspection.gc.ca/plants/plants-with-novel-traits/general-public/data-required/eng/1338148160172/1338148232049

[30] Guidelines for the Assessment of Novel Feeds: Plant Sources http://www.inspection.gc.ca/animals/feeds/regulatory-guidance/rg-1/chapter-2/eng/1329298059609/1329298179464?chap=6

[31] Guidelines for the Safety Assessment of Novel Foods: https://www.canada.ca/content/dam/hc-sc/migration/hc-sc/fn-an/alt_formats/hpfb-dgpsa/pdf/gmf-agm/guidelines-lignesdirectrices-eng.pdf

- The regulatory status of nGM applications is determined for each individual product, similar as for applications developed by other methods, like GM technology. Decisions for non-regulated status are not publicly disclosed at present.
- A number of “novel” nGM plants were authorised as PNTs, further nGM applications are currently risk assessed according to the existing case-specific approach. No (GM-) labelling is required for regulated products, including nGM plants. Detection and traceability requirements are not an issue in Canada.
- In the future a simplified risk assessment approach for low-risk applications may be proposed. Authorities discuss sets of formal criteria for such a regime as well as for the evaluation of the regulatory status of products.

3.6 Argentina

3.6.1 Main features of the Argentinian regulatory framework

Existing legislation

Argentina introduced a national „Regulation Framework for Agricultural Biotechnology” in 1991 and is therefore recognized as a country which established a functional regulatory system quite early (LEMA 2019, WHELAN&LEMA 2015). The Argentinian regulations are considered to be compatible with the CPB, although the national legislation was enacted prior to the CPB and Argentina is not a Party to the CPB (LEMA 2019, WHELAN&LEMA 2015).

A revised regulatory framework was implemented in 2012 to improve the efficiency of the existing regulatory procedures. The revision was initiated primarily to address the issue that the time necessary to obtain regulatory approval was considered too long by stakeholders (YANKELEVICH 2014).

One pillar of the revised regulation framework is Resolution (SAGYP) No. 701/2011 (27.10.2011), which sets forth the requirements that must be met for the release of GM plants into the environment. The Resolution also specifies the regulatory procedures for the authorisation of such applications. Other pieces of legislation are addressing the regulation of GM microorganisms and viruses, as well as GM animals.

Involved authorities

The main authority responsible for the regulation and authorization of crops developed by biotechnology is the Ministry of Agriculture, Livestock and Fisheries (MAGYP). The MAGYP, in particular its Biotechnology Directorate (BD) is responsible for three areas: biosafety issues, policy analysis & formulation and regulatory design (YANKELEVICH 2014). The BD acts as the primary regulatory agency for regulated GM crops and for the biosafety evaluation according to Resolution (SAGYP) No. 701/2011.

Prior to authorization of crops for commercial use, e.g. for cultivation and for marketing of products derived from them, MAGYP is requesting an opinion on the specific application from the following three regulatory agencies (SCHUTTELAAR 2015):

- The National Advisory Commission on Agricultural Biotechnology (CONABIA). The tasks of CONABIA regarding the scientific risk assessment of GMO applications and the design of biosafety and risk management measures are specified by Resolution

(SAGYP) No. 437/2012, Article 3. The Biotechnology Directorate is acting as the executive secretariat for CONABIA supporting its biosafety-related tasks according to Article 3.A of Resolution No. 763/2011 (LEMA 2019).

- The National Service of Agrifood Health and Quality (SENASA), supported by the Food and Feed Safety Advisory commission (TAC), which is responsible for food and feed safety;
- Directorate of Agricultural Markets (DNMA), which is responsible for the assessment of impacts of the application of regulated products on trade and production.

Authorization is only granted if opinions of all of the three involved bodies are in favour of an approval of a specific application.

Regulatory approach

According to the definition contained in Resolution (SAGYP) No. 701/2011 the scope of the legislation is encompassing all GM plant events, which do contain novel combinations of genetic material due to the application of techniques of modern biotechnology. The term "novel combination of genetic material" is defined in Resolution (SAGYP) No. 701/2011 as "combined and stable insertions into the plant genome of one or more genes or DNA sequences that are part of a defined genetic construct". This definition is considered to be compatible with the approach used in the CPB to define the scope of regulations (SCHUTTELAAR 2015). The regulatory approach implemented in Argentina is therefore comparable to the approach implemented in the EU, with a definition which is also referring to the technological process of genetic modification used to generate specific biotechnology products. The Argentine system therefore is implementing a process-oriented definition to trigger regulatory requirements.

It is noteworthy that previous reviews concluded that the system is implemented with a "product-oriented approach during regulatory analysis", since the principles enshrined in the regulation, among them the case-by-case principle would emphasize such an approach (SCHUTTELAAR 2015). This conclusion however confuses the fact that a product-by-product consideration required by a regulatory framework can be based on a process-oriented trigger, which defines the scope of regulated products (YANKELEVICH 2016).

However the term "novel combinations of genetic material" was debated since its interpretation was regarded as crucial to answer the question whether a product developed by nGMs would be considered a GMO subject to the existing regulatory framework or not (WHELAN&LEMA 2015).

3.6.2 Coverage of nGMs by the Argentinian regulatory framework

A specific resolution (Resolution No. 173/2015) was published in 2015 by the MAGYP to establish criteria for case-by-case decisions, whether a specific crop which was developed by techniques involving modern biotechnology is considered to be subject to the existing GMO regulations (LEMA 2019, WHELAN&LEMA 2015). Comparable legislation which is compatible with the principles of Resolution No. 173/2015 was introduced by other South American countries subsequently, specifically by Brazil, Chile, and Colombia (LEMA 2019).

The respective considerations for these decisions focus on the question whether a new combination of genetic material as defined by Resolution (SAGYP) No. 701/2011 is present in the crop under review. In this context the issue is also addressed whether transgenes were only present temporarily in the respective nGM crop. If scientific evidence is presented that such transgenes are no longer present in the final breeding product the crop is not considered to be subject to GMO regulations.

Several types of nGM applications (Genome editing by SDN-1, SDN-2, SDN-3 and ODM; cisgenesis/intragenesis, agroinfiltration, transgrafting, reverse breeding and RdDM) were reviewed prior to the establishment of the resolution by CONABIA to indicate whether the respective techniques are likely to generate products that would be considered as GMOs according to the legislation (SCHUTTELAAR 2015). However actual decisions are only made case-by-case upon submission of an application for a specific product by the applicant to the authorities and after a preliminary review conducted by the BD within 60 days.

In their submissions applicants shall notify information on the breeding methodology used to generate and select the new crop, on the new traits or characteristics introduced into the crop and on evidence of genetic changes present in the final breeding product. The information is used by CONABIA to assess whether a new combination of genetic material according to the definition of the regulatory trigger has been created (Resolution No. 173/2015, Article 4). The results of the scientific assessment of the submitted information by CONABIA are considered by the BD for determination whether the specific product would be regarded to be a regulated as a GMO according to Resolution No. 763/2011 and complementary legislation (Resolution No. 173/2015, Article 5).

According to Article 7 of Resolution No. 173/2015, applicants may file preliminary inquiries whether products developed by a specific nGM approach would likely fall under the scope of Resolution No. 763/2011. CONABIA then will perform a preliminary technical assessment and provide an indicative opinion to the question. However this preliminary conclusion must be confirmed by the authorities after the new crops were obtained based on information submitted for the actual plant product (WHELAN&LEMA 2015). According to LEMA (2019) most of the nGM products notified since implementation of Resolution No. 173/2015 were submitted at the design stage by means of preliminary inquiries.

Products that are determined to not fall under the GMO regulations are still subject to the requirements and standards for new crop varieties, which are also enforced by the MAGYP. If significant risks are found to be associated with such crops notice must be made in the decision and the variety regulators need to be informed (WHELAN&LEMA 2015).

3.6.3 **Risk assessment requirements for GMOs and nGM applications**

Risk assessment requirements for GMOs

A pre-marketing risk assessment is conducted upon an application for authorization of a specific GMO product according to Resolution (SAGYP) No. 701/2011. As indicated above CONABIA is providing technical support concerning the necessary risk evaluation to the BD.

The evaluation of GM events takes place on a case-by-case basis, taking into consideration the characteristics of the GM plant as well as potential adverse effects on the health of humans or animals, as well as adverse impacts on the environment and the agricultural

production (YANKELEVICH 2016). Regarding the biotechnological processes used to obtain the GM event in question, respective differences between the GM event and a comparable non-GM organism (conventional counterpart) are considered with respect to the effects resulting from these differences on the agro-ecosystem as well as on its safety as food or feed for human or animal consumption (YANKELEVICH 2016).

Risk assessment requirements for nGM applications

Similar standards for risk assessment as specified in Resolution (SAGYP) No. 701/2011 are implemented for GMOs and nGM applications which are determined to be subject to the GMO regulations according to Resolution No. 173/2015.

For new crops which are not considered to fall under the GMO regulations, any potential for significant adverse effects associated with the crop which is identified during the review according to Res. No. 173/2015 needs to be notified to the regulators for non-GM crop varieties for further consideration (WHELAN&LEMA 2015). According to a 2016 revision of the Argentine Seed Law, the National Seed Institute (INASE) is designated as the national authority to establish particular requirements for registration in the National Registry of Cultivars. The recommendations by CONABIA for follow-up measures derived from the review according to Resolution No. 173/2015 described above are forwarded to INASE for consideration.

3.6.4 Outstanding aspects of the existing regulatory framework in Argentina

- A process-oriented regulation framework with a regulatory trigger based on the definition contained in the CPB is in place since 1991 for sectoral regulation of GMOs. This biosafety law was revised in 2012.
- A supplementary regulation to introduce a procedure and criteria for the determination of the regulatory status of biotechnology applications including nGM products was implemented in 2015. Argentina was the first country to introduce such supplementary regulations addressing the regulatory status of nGM products.
- Until 2019 a number of applications for nGMs were submitted for review; some from foreign multinational companies and a larger number by national public research institutions and small and medium sized national enterprises (LEMA 2019).
- No specific risk assessment requirements apply to nGM applications in comparison to GMOs.

3.7 Brazil

3.7.1 Main features of the Brazilian regulatory framework

Existing legislation

Brazil introduced its first regulations for GM-foods and -plants in 1995. However the legislation and its implementation were challenged in court as violating the national environmental laws (NAS 2016). After extensive discussions concerning, inter alia, the regulatory responsibilities of involved authorities and the way of decision making, a new biosafety framework was implemented in 2005, by the adoption of the Brazilian Law No.

11.105. The new biosafety law which is compatible with the CPB was amended in 2006 by Decree No. 5591 and in 2007 by Law No. 11.460. Several normative resolutions were enacted subsequently to guide different aspects of the implementation of the biosafety law. In 2018 normative resolutions No. 16 was adopted which is outlining the procedure and the criteria to determine the regulatory status of nGM applications, which are called Precision Breeding Innovation Techniques (PBIT) in the resolution (LEMA 2019).

The legislation provides a framework for the authorization procedure to be conducted for regulated products, their assessment prior to authorization regarding biosafety and non-biosafety issues. The framework also includes measures concerning coexistence of cultivation of GM- and non-GM crops, provisions regarding liability for damages caused to third parties and the environment and a labelling regime for GM foods and food ingredients (NAS 2016).

Involved authorities

The Ministry for Agriculture, Livestock and Supply (MAPA) is responsible for regulation, registration and inspection of research into new crops and of commercial application of new crops. MAPA is cooperating with the Ministry of Health regarding food safety issues and the Ministry for the Environment for matters concerning environmental protection, e.g. in the framework of the National Biosafety Council and at a technical level concerning risk assessments (SCHUTTELAAR 2015).

Two bodies are specifically important for the implementation of the Brazilian GMO regulations:

- The National Biosafety Council (CNBS), a political body of cabinet ministers.
- The National Technical Commission on Biosafety (CTNBio), an expert body established by the Ministry of Science and Technology, which is providing technical support for the decision-making on product notifications.

The National Biosafety Council (CNBS) is responsible for developing an overall national biosafety policy and its implementation. In its opinions CNBS shall consider biosafety aspects as well as national and socioeconomic implications of agricultural biotechnology (NAS 2016, SCHUTTELAAR 2015) The Brazilian Biosafety Law designates CNBS as the final decision-making authority concerning the authorization of particular GMOs for commercialization and environmental release.

The National Technical Commission on Biosafety (CTNBio) addresses technical issues, including the risk assessment conducted to identify environmental as well as food-safety related risks of GMOs for environmental release and import. The commission consists of members appointed by the federal ministries, technical specialists and experts representing consumers and farmers (NAS 2016), the meetings are open to the public and recommendations need to be supported by a majority of commission members (NAS 2016).

In regulatory practice the CNBS is following the recommendations by CTNBio concerning biosafety issues and only deviates from these recommendations, if important considerations like national interests and socio-economic aspects are concerned. CTNBio is not involved in the technical preparation of socio-economic assessments (NAS 2016). Social and economic issues are considered by the commission, which consists of 27 members among them representatives from the Ministries of Agriculture, Health, and Environment and members

from universities and research institutions (EMBRAPA pers. comm.). In this way the technical risk assessment is separated from the consideration of non-biosafety issues.

Regulatory approach

Article 3 of the Brazilian Biosafety Law No 11.105 defines the scope of the law, which includes all organisms whose genetic material (DNA or RNA) has been modified by any genetic engineering technique (Article 3, Para. V). Genetic engineering is defined as "the production and manipulation of recombinant DNA/RNA molecules" according to Article 3 (Para. IV). As outlined in Para. III of Article 3 this is covering techniques, which involve DNA/RNA molecules manipulated outside living cells through changes made to natural or synthetic DNA/RNA segments that are introduced into a living cell and which can be further propagated in those cells [32]. It is noteworthy that the nature of the particular modification(s) is not referred to by the definition (NAS 2016).

Products obtained from a GMO according to the above definition, which do not contain viable GM organisms or do not have autonomous replication capacity are defined as GM by-products/derivatives (Article 3, Para. VI).

Since the definition used by the Brazilian Biosafety Law is focused on the way in which a genetic modification is introduced, the regulation is regarded to be process-oriented. The definition of what is considered "any genetic engineering technique" is regarded to be quite general and broad (SCHUTTELAAR 2015).

Plants developed by classical mutation breeding not involving GM technology and by cell fusion techniques resulting in products, which could also be established by conventional breeding approaches are not regulated under Biosafety Law No 11.105 (Article 4). As a result herbicide resistant (HR) crops developed by these methods are not regulated like GM-HR plants.

For applications regarding authorisation of crop plants covered by the definition a dossier needs to be submitted to CTNBio containing the required information: i.e. scientific information describing the process of modification, the respective specific genetic modification(s) which and the effects resulting from them (NAS 2016).

GMO products need to be labelled with a symbolic label (yellow triangle with letter "T" for "transgenico") in Brazil, however public awareness of the GM label is considered to be limited (EMBRAPA Pers. Comm.).

3.7.2 Coverage of nGMs by the regulatory framework in Brazil

The Brazilian authorities were aware of the issue, that the trigger definition introduced with the Brazilian biosafety law in 2005 was not ideally suited to address emerging technologies like some nGMs. In particular the regulatory status of nGM applications, which require the creation of a GM plant at an intermediary step, but which result in final products carrying

[32] Biosafety Law No 11.105, Article 3 (III) – Recombinant DNA/RNA molecules refers to molecules that are manipulated outside living cells by altering natural or synthetic DNA/RNA segments and that can multiply themselves in a living cell, or the DNA/RNA molecules resulting from this multiplication; they also refer to the synthetic DNA/RNA segments equivalent to natural DNA/RNA segments

mutations at specific genomic locations (e.g. small deletions) was actively debated, e.g. in the CTNBio.

In January of 2018 a new normative resolution addressing the issue for nGMs which was developed by CTNBio was enacted (normative resolution No. 16, Jan. 15th, 2018 on the technical requirements for submitting an inquiry to the CTNBio concerning Precision Breeding Innovation Techniques). This resolution is based on the respective regulations, which were implemented in Argentina (see chapter 3.7.1).

According to the new framework a case-by-case decision needs to be made, whether a specific (nGM) application is subject to the GMO regulations. The term PBIT comprises a broad range of (nGM) applications, e.g.

- targeted genome editing,
- genetic or epigenetic modification of gene expression (activation, silencing),
- cisgenesis (genetic transformation and/or control of gene expression with genes of sexually compatible species),
- temporary and not-heritable genetic modifications,
- gene drive applications and construction of heterologous genes or new copies of homologous genes
- permanent or non-host infection of genetically modified viral elements

A non-exhaustive list of nGM applications is included in the normative resolution for reference, which is listing a number of existing applications (precocious flowering, seed producing technology, reverse breeding, RNA-dependent DNA methylation, Site-directed mutagenesis and oligonucleotide directed mutagenesis, agroinfiltration/agroinfection, topical/systemic use of RNAi, use of viral vectors).

Individual PBITs may be exempted by CTNBio from regulation according to the biosafety law after an assessment considering a number of criteria. Specifically products that show at least one of the following characteristics may be exempted:

- Product with proved lack of recombinant DNA/RNA, obtained with a technique using parental GMO;
- Product obtained through a technique using DNA/RNA which will not multiply in a living cell;
- Product obtained by a technique which introduces site-directed mutations such as SDN-1, SDN-2 or ODM applications inducing genetic function gain or loss, but proved absence of recombinant DNA/RNA in the product;
- Product obtained by a technique in which there is temporary or permanent expression of recombinant DNA/RNA molecules, but no presence or introgression of these molecules in the product;
- Product which uses techniques employing DNA/RNA molecules that do not modify permanently a plant's genome when in contact, or systemically or non-systemically absorbed by it.

The determination of the regulatory status of nGM applications under the existing legislation is not subject to a pre-evaluation of specific risks associated with these applications.

Applications which are determined not to fall under this framework are subject to the general requirements according to environmental, phytosanitary and agricultural regulations. The MAPA is the responsible authority for phytosanitary issues and general quality standards required for registration of crop varieties; the Ministry of the Environment reviews compliance with environmental regulations and the Ministry of Health is responsible for food safety issues (SCHUTTELAAR 2015).

The requirements for variety registration are based on criteria concerning the distinctiveness, uniformity and stability of new varieties (DUS criteria) (EMBRAPA pers. comm.).

3.7.3 Risk assessment requirements for GMOs and nGM applications

Risk assessment requirements for GMOs

CTNBio is responsible for carrying out a risk assessment of environmental risks and food safety issues prior to the authorization of a GMO or GM by-products/derivatives according to Article 3, Para VI of the Biosafety Law. The assessment is based on information submitted to CTNBio by the applicant, which needs to be approved and reviewed by an internal Biosafety Committee (CIBio) set up by the applicant (NAS 2016).

According to the Normative Resolution No. 5, Article 6(I) applications for commercial introduction need to be assessed for potential adverse effects of the crop and its by-products on human and animal health and on plants and the environment by CTNBio. The evaluation shall be conducted in a transparent and scientific manner, which takes into account the precautionary principle (NAS 2016). The resolution includes criteria for the risk assessment and specific risk management requirements, e.g. protection distances for certain plant species.

An additional Normative Resolution by CTNBio provides guidance regarding the information which needs to be submitted. Normative Resolution No. 6 Annexes I – IV) contains specifics on the information, which needs to be submitted for application, i.e. information to describe the modification(s) present in the notified plant and the process which was used to generate the respective plant, including the recombinant sequences introduced. In addition data on the phenotypic effects of the modification need to be generated during field testing which needs to be conducted in different regions in Brazil.

The food safety assessment conducted by CTNBio is based on the respective guidelines of the Codex Alimentarius Commission (NAS 2016).

In addition CTNBio can ask for more information based on a request of any CTNBio-member and a respective majority decision of CTNBio. Before the final decision the application is discussed in the commission. Based upon the opinion of CTNBio the Ministry of Agriculture can require risk management measures, e.g. to preserve the efficacy of the technology. For example refuge areas for Insect-resistant Bt-crops to prevent the development of Bt-resistant pest insects are requested (EMBRAPA pers. comm.).

Since 2007 all GMO-applications have to undergo a follow-up monitoring for 5 years. The current monitoring approach is based on interviews with users of the products to identify whether any adverse effects were observed.

Risk assessment requirements for nGM applications

nGM applications which are determined to fall under the GMO regulations are assessed according to similar standards as GMOs as described above. Monitoring requirements will only apply if nGM applications are subject to current biosafety law; no comparable monitoring requirements exist for non-GM applications.

3.7.4 Outstanding aspects of the existing regulatory framework in Brazil

- The current biosafety framework was introduced in 2005 and is compatible with the CPB. Additional regulatory requirements other than risk assessment include provisions for monitoring, coexistence, liability and labelling of GM foods.
- The regulations are triggered by a process-oriented definition, which in a broad sense covers any technologies based on the use of recombinant nucleic acids.
- A supplementary regulation, i.e. a normative resolution, addressing nGM applications was adopted in January of 2018. It outlines the criteria and process for the determination of the regulatory status of PBITs which is conducted by the national technical biosafety commission (CTNBio).
- GMOs and nGM applications covered by the biosafety law need to undergo a risk assessment of environmental and health effects conducted by the CTNBio, the national biosafety commission. In addition an independent consideration of socio-economic effects may be conducted; however such an evaluation is performed only rarely.

3.8 Australia

3.8.1 Main features of the regulatory framework

Existing legislation

Biotechnology applications in Australia are regulated by the Gene Technology Act (GTA) 2000[33] and the Gene Technology Regulations (GTR) 2001[34]. They provide the legal basis for the regulation of both GMOs and nGMs, which meet the definitions included in the mentioned act and the regulations. Regulated items according to the act are ‘dealings’ (defined activities) with organisms that have been modified by gene technology, as well as their progenies, if they inherit the traits introduced by gene technology. In addition any other organisms which are specifically identified as GMOs by the regulations are also covered.

The GTR also list organisms that are not considered to be GMOs. Those are among others mutant organisms, in which the mutational event did not involve the introduction of any

[33] https://www.legislation.gov.au/Series/C2004A00762

[34] https://www.legislation.gov.au/Series/F2001B00162

foreign nucleic acid. Furthermore organisms that result from an exchange of DNA are excluded from regulation if both of the following two requirements are met:

- the DNA is derived from the same species and
- the vector used does not contain any heterologous DNA sequences.

A detailed list of specifically excluded organisms is included in Schedule 1 of the GTR[35].

Gene technology as mentioned in the above definition is described in the act as follows: "*gene technology means any technique for the modification of genes or other genetic material*". Not included are genetic changes introduced by sexual reproduction, homologous recombination or any other technique specified in the regulations in relation to this definition (*inter alia* mutagenesis introduced by chemical agents, particle radiation or electromagnetic radiation or a natural process, when no genetically modified material is involved). The specific exclusions are listed in Schedule 1A of the GTR[36].

To address matters of regulation which are within the responsibility of the Australian States the Gene Technology (Recognition of Designated Areas) Principle 2003[37] was developed in accordance with the GTA. This Principle ensures that the designation of special areas for either GM- or non-GM crops for market purposes under state and territory law can be implemented in consistency with the regulation of the respective applications at the level of the Australian Commonwealth.

Involved authorities

The Australian Gene Technology Regulator is responsible for regulation and approval of existing and novel crops. Regulatory agencies related to the authorisation of commercial crop cultivation and respective products are the Office of the Gene Technology Regulator (OGTR), Food Standards Australia New Zealand (FSANZ) and the Australian Pesticides &

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[35] (1) A mutant organism in which the mutational event did not involve the introduction of any foreign nucleic acid (that is, non-homologous DNA, usually from another species). (2) A whole animal, or a human being, modified by the introduction of naked recombinant nucleic acid (such as a DNA vaccine) into its somatic cells, if the introduced nucleic acid is incapable of giving rise to infectious agents. (3) Naked plasmid DNA that is incapable of giving rise to infectious agents when introduced into a host cell. (4) An organism that results from an exchange of DNA if (a) the donor species is also the host species; and (b) the vector DNA does not contain any heterologous DNA. (5) An organism that results from an exchange of DNA between the donor species and the host species if (a) such exchange can occur by naturally occurring processes; and (b) the donor species and the host species are microorganisms that: (i) satisfy the criteria in AS/NZS 2243.3:2010 for classification as Risk Group 1; and (ii) are known to exchange nucleic acid by a natural physiological process; and(c) the vector used in the exchange does not contain heterologous DNA from any organism other than an organism that is involved in the exchange.

[36] (1) Somatic cell nuclear transfer, if the transfer does not involve genetically modified material. (2) Electromagnetic radiation-induced mutagenesis. (3) Particle radiation-induced mutagenesis. (4) Chemical-induced mutagenesis. (5) Fusion of animal cells, or human cells, if the fused cells are unable to form a viable whole animal or human. (6) Protoplast fusion, including fusion of plant protoplasts. (7) Embryo rescue. (8) In vitro fertilisation. (9) Zygote implantation. (10) A natural process, if the process does not involve genetically modified material (e.g. conjugation, transduction, transformation and transposon mutagenesis)

[37] Commonwealth Government Special Gazette No. S340 (5 September 2003)

Veterinary Medicines Authority (APVMA). The OGTR is only concerned with GMOs (SCHUTTELAAR 2015).

FSANZ is a bi-national government agency, since Australia and New Zealand cooperate closely regarding food safety and its regulation[38]. While Australia and New Zealand share a food regulatory system, each country has its own system for assessing potential environmental risks arising from the use of GM organisms. Approvals to grow GM crops in Australia fall within the responsibilities of the OGTR[39]. Approval by both FSANZ and the OGTR is necessary before a GM food crop may be commercially produced and/or used in food production in Australia. Most of the approvals for GM food granted by FSANZ relate to imported materials, like non-viable foods ingredients, which are not produced from plants cultivated in either Australia or New Zealand.

The Legislative and Governance Forum on Gene Technology (LGFGT), which was formerly referred to as the Gene Technology Ministerial Council, is responsible for policy development and the consistent implementation of the regulatory framework by both the Australian Commonwealth and the involved Australian states and territories. It is composed of a Commonwealth minister and one Minister of each of the eight Australian states. One of the responsibilities of the LGFGT is the regular review of the existing regulatory framework for needs of adaptation or revision. Currently the third general review the national Gene Technology Scheme, is under way (LGFGT 2018). The Scheme consists of the Gene Technology Agreement 2001, which provides the mechanisms for cooperation of all involved institutions of State, Territory and Commonwealth governments, as well as the GTA, the GTR and corresponding state and territory legislation.

Regulatory approach

As mentioned above the Australian GTA sets the regulatory frame for gene technology. The regulatory system is using a process-oriented trigger. Respective applications are assessed and licenced by OGTR on a case-by-case basis focusing on the product characteristics and the features of the resulting organism.

Regarding the determination of the regulatory status for matters requiring clarification, OGTR can only provide case-by-case advice[40], but no legally binding decisions concerning the question, whether or not a specific biotech application falls within the regulatory scope of the GTA. In the past, however, there have never been unresolvable disputes between the authority and the developers concerning this question. The GTA and guidance provided by OGTR seems to be sufficiently clear to avoid such disputes and technical questions could be resolved by consultation between applicants and authority. Therefore no court proceedings were ever initiated to address a pending dispute concerning the regulatory status of a specific application (OGTR pers. comm.).

According to Section 1.1.1-10 of the Australian and New Zealand Food Standards Code all GM foods are subject to a pre-market assessment by FSANZ to determine their safety for

[38] Information on FSANZ is relevant for both Australia and New Zealand. However, in order to avoid duplications, respective details are only provided in chapter 3.8

[39] See http://www.ogtr.gov.au

[40] further information is available at:
http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/newtechnologies-htm

human consumption before they are permitted on the market. The determination of the regulatory status is based on the definitions of "food produced using gene technology" and "gene technology as given by Section 1.1.2-2 of the Food Standards Code (the Code). These definitions are considered to constitute a process-based regulatory trigger and were not changed for almost 20 years (FSANZ 2018)[41]. FSANZ also regulates other novel foods, however under a separate standard. Approval is necessary both for foods produced in Australia (or New Zealand), and for foods imported from other countries (OECD 2015).

Since the adoption of Standard 1.5.2 – Food produced using gene technology more than seventy foods have been assessed, approved and listed in Schedule 26 of the Code (FSANZ 2018). Approved GM food and ingredients that contain novel DNA or novel protein(s) need to be labelled. The respective definition is contained in the Standard 1.5.2 of the Code. In addition labelling is required for GM food with altered characteristics in comparison to a non-GM food counterpart.

3.8.2 Coverage of nGMs by the Australian regulatory framework

In Australia no specific regulations exist for nGMs. As mentioned above nGM applications are in principle covered by the existing legislation described. However, a future approach towards regulation of nGMs which is based on a review of the existing regulations by both OGTR and FSANZ is currently developed. While a technical revision proposed by the OGTR on their parts was enacted in April 2019[42], FSANZ started consultations in February 2018 directed to consider issues related to possible future changes of the Code (FSANZ 2018) and delivered a final report on their review of food derived using new breeding techniques in December of 2019[43]. Matters of overall biotechnology policy are addressed by the third general review of the GT scheme (LGFGT 2018).

Approach by OGTR

The OGTR initiated a technical review of the GTR with the aim of clarifying the regulatory status of nGMs, in particular of genome editing applications[44] . For this process a respective discussion paper was published (OGTR 2016). In this paper four possible options for the regulation of several specific nGMs were proposed:

- Option 1 (according to OGTR): No amendment of current legislation.
- Option 2 (according to OGTR): Regulation of organisms modified using all new techniques included in the review (i.e. SDN-1 and SDN-2 site-directed nuclease techniques, ODM).

[41] "food produced using gene technology means a food which has been derived or developed from an organism which has been modified by gene technology; gene technology means recombinant DNA techniques that alter the heritable genetic material of living cells or organisms"

[42] https://www.legislation.gov.au/Details/F2019L00573

[43] https://www.foodstandards.gov.au/consumer/gmfood/Pages/Review-of-new-breeding-technologies-.aspx

[44] Technical Review of the Gene Technology Regulations 2001: http://www.ogtr.gov.au/internet/ogtr/publishing.nsf/Content/reviewregulations-1

- Option 3 (according to OGTR): Regulation of organisms modified using SDN-2 and ODM, and exclusion of organisms modified using SDN-1 from regulation.
- Option 4 (according to OGTR): Exclusion of organisms modified using SDN-1, SDN-2 and ODM from regulation.

Following consultations with stakeholders, the OGTR proposed amendments to the existing regulations based on the notion that option 3 best supports the effectiveness of the legislative framework at this time. Under option 3 organisms modified using site-directed nucleases without templates to guide genome repair (i.e. SDN-1) would not be regulated as GMOs. Currently, if a template is used to guide genome repair (i.e. SDN-2 and SDN-3), the resulting organisms are GMOs, as are organisms modified using ODM. These would continue to be regulated under this option.

The amendment implementing option 3 was enacted with the Gene Technology Amendment (2019 Measures No. 1) Regulations 2019 in April of 2019. Under the amendments, the application of synthetic RNA molecules to organisms to induce RNAi is not be regulated as gene technology, provided that the RNA cannot give rise to changes to genomic sequence and cannot be translated into proteins. However RNAi techniques which involve inserting sequences into the genome or the use of viral vectors would continue to result in GMOs which are subject to regulation.

Furthermore, and in addition to the above issues of the review, a mandatory requirement for licencing all contained dealings with all GMOs modified to contain gene drives is included.

Approach by FSANZ

Since neither the technical review conducted by the OGTR nor the third review of the National Gene Technology Scheme implemented by the GTA and the GTR addresses gene technology related issues of the food standards code, FSANZ needs to develop a separate approach to revise of its current regulatory Food Standard in parallel.

FSANZ organized a series of expert workshops addressing the issue of nGMs in 2012 and 2013 to understand which types of foods that may result from their use. The review focused on a number of nGM applications, in particular genome editing, GM rootstock grafting, cisgenesis and intragenesis and techniques producing null-segregants.

FSANZ concluded that applications for genome editing, GM rootstock grafting and techniques producing null-segregants are generating the most uncertainty with respect to the definition for '*food produced using gene technology*' (FSANZ 2018). Therefore the consultation is addressing a number of questions relating to these uncertainties:

- whether foods derived from organisms containing newly introduced DNA (incl. cisgenic organisms or plants developed by grafting on GM rootstock) should be subject to risk assessment and approval,
- whether foods derived from null-segregants should be excluded from the current requirements for risk assessment and which criteria should be used for the conditional exclusion of such products,
- which differences and similarities of genome editing compared with classical methods of mutagenesis are perceived and which applications of genome editing might carry risks that warrant a requirement for risk assessment.

An overarching question of the review addresses the question whether a process-oriented trigger for regulation is appropriate for nGM applications and how the current definitions could be adapted to better accommodate nGMs (FSANZ 2018).

The current policy review does not consider issues related to the current labelling of GM foods. Based on the results of the review FSANZ will prepare a proposal to amend the existing Code and will further consult with the public on the proposal in 2020 (FSANZ 2018).

3.8.3 Risk assessment requirements for GMOs and nGM applications

Risk assessment required for GMOs

Risk assessment of applications for environmental release

In order to release GMOs into the environment or for the use of specified GMOs in contained use a licence is required. This licence is issued by the Gene Technology Regulator on a case-by-case basis that also includes the assessment of risks. The procedure is laid down in the GTA and GTR; specifics are provided by the Risk Analysis Framework (OFFICE OF THE GENE TECHNOLOGY REGULATOR 2013). The latter document also outlines the preparation of risk management plans, licence conditions and communication with stakeholders.

In this framework general information is provided on the considerations for the risk assessment and respective steps (risk identification, consequences assessment, likelihood assessment, risk evaluation). According to the framework (chapter 4), the establishment of the risk assessment context includes information on genotype, phenotype, the intended use, the receiving environment, parent organism and information regarding previous releases. In addition a list of other factors that might be relevant for risk scenarios is provided (e.g. survival and persistence, altered biochemistry gene transfer or unauthorised activities).

Risk assessment of applications for food safety

The regulation of GM food is provided for in Standard 1.5.2 – Food produced using Gene Technology of the Australia New Zealand Food Standards Code (OECD 2015). The procedures implemented for risk assessment of regulated foods are consistent with the guidelines and principles developed by the Codex Alimentarius Commission for GM food safety assessments.

In 2015 FSANZ undertook a review of its safety assessment guidelines and data requirements for GM foods as part of a broader review of its data and information requirements contained within Part 3 of the FSANZ Application Handbook. As a result of this review, and subsequent public consultation, FSANZ made significant amendments to the Handbook, including the data requirements for GM foods (FSANZ 2016).

In relation to GM foods, the data requirements (Guideline 3.5.1) have been substantially updated to reflect recent scientific developments, improve clarity and transparency, remove superfluous requirements and introduce a more streamlined form of safety assessment approach for those products which are known through prior knowledge, evidence and experience to be lower risk (FSANZ 2016).

Risk assessment required for nGMs

If a nGM application is determined to fall under the GMO regulations, the same respective risk assessment standards would apply as for any other item regulated by the GTA. This would also be the case in relation to food products assessed under Standard 1.5.2 of the Food Standards Code.

In case nGM applications would not be regarded as GMOs, general requirements would apply, e.g. measures according to the existing quarantine regulations and concerning variety registration (OGTR, pers. comm.).

In the case of foods not captured under Standard 1.5.2 of the Food Code, the general provisions of food law, which require food to be safe and suitable as well as the general food labelling provisions would still apply. As described by SCHUTTELAAR (2015) biotech food products which are determined to be non-GM are not automatically captured by the Novel Foods Standard. A safety assessment according to the Novel Foods Standards is only conducted if the substantive nature of the food has been changed.

3.8.4 Outstanding aspects of the existing regulatory framework in Australia

- The regulatory framework consists of sectoral legislation for either environmental release of GMOs and consumption and labelling of GM foods, respectively, involving two main statutory authorities at the commonwealth level (OGTR and FSANZ). Additional requirements in relation to specific areas for release may be determined at the level of the Australian States.
- The regulations are based on process-oriented regulatory triggers (their wording however is slightly different in GTA and GM food standards code). Triggers are supplemented by lists of specific techniques which are exempt of regulation.
- The status of regulation needs to be determined by the developer of the product; OGTR can be consulted for advice.
- Three separate policy reviews were initiated, which are partly triggered by regulatory issues due to emerging nGM applications: a general review of the national GT scheme, a technical review of the trigger definitions, which led to amendments in April 2019 included the GTA and GTR and a review of provisions the food code which relate to GM foods.
- According to the 2019 amendment SDN-1 applications are not regulated according to the GTA, as well as organisms derived from GMOs but in which the modification and any transgenic traits are no longer present. In addition some RNAi techniques are not regarded gene technology. Applications which use recombinant nucleic acid templates to direct genetic modifications, such as SDN-2, SDN-3 and ODM applications on the other hand are regarded to be GMOs and regulated by the GTA.

3.9 New Zealand (NZL)

3.9.1 Main features of the NZL regulatory framework

Existing legislation

Biotechnology applications in plant breeding are regulated together with hazardous substances by the "Hazardous Substances and New Organisms Act 1996" (HSNO)[45], most recently amended in 2015, and the Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations 1998[46], most recently amended in 2016. GMOs are a specific class of "new organisms" that are the subject of the legislation (other organisms covered are inter alia species that were not present in New Zealand before 29 July 1998). A detailed description of what is considered a new organism according to the HSNO Act is included in the act under Part 1, Section 2A(1)[47].

The HSNO Act also sets out which organisms are not considered to be "new organisms" according to the HSNO regulations. Of particular interest for this study is that specific types of GMOs are exempted from regulation. Exempted are GMOs which were not considered to be a GMO according to HSNO previously or which are similar to organisms for which permission to release has been granted (i.e. organisms of the same taxonomical unit which contain the same genetic modification as the organism in question). This definition is also included in the HSNO act under Part 1, Section 2A, subsection (2)[48].

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[45] http://www.legislation.govt.nz/act/public/1996/0030/latest/DLM381222.html

[46] http://legislation.govt.nz/regulation/public/1998/0219/latest/DLM255883.html?src=qs

[47] A new organism is "(a) an organism belonging to a species that was not present in New Zealand immediately before 29 July 1998: (b) an organism belonging to a species, subspecies, infrasubspecies, variety, strain, or cultivar prescribed as a risk species, where that organism was not present in New Zealand at the time of promulgation of the relevant regulation: (c) an organism for which a containment approval has been given under this Act: (ca) an organism for which a conditional release approval has been given: (cb) a qualifying organism approved for release with controls: (d) a genetically modified organism: (e) an organism that belongs to a species, subspecies, infrasubspecies, variety, strain, or cultivar that has been eradicated from New Zealand"

[48] An organism is not a new organism if:

"(a) the organism is not a genetically modified organism and (i) an approval is granted under section 35 or 38 to release an organism of the same taxonomic classification; or (ii) the organism is a qualifying organism and an approval has been granted under section 38I to release an organism of the same taxonomic classification without controls; or (iii) an organism of the same taxonomic classification has been prescribed as not a new organism; or

(b) the organism is a genetically modified organism and (i) an approval is granted under section 38 to release an organism of the same taxonomic classification with the same genetic modification; or (ii) the organism is a qualifying organism and an approval has been granted under section 38I to release an organism of the same taxonomic classification with the same genetic modification without controls; or (iii) an organism of the same taxonomic classification with the same genetic modification has been prescribed as not a new organism; or

(c) the new organism was deemed to be a new organism under section 255 and other organisms of the same taxonomic classification were lawfully present in New Zealand before the commencement of that section and in a place that was not registered as a circus or zoo under the Zoological Gardens Regulations 1977"

Additionally the Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations 1998, Section 3 lists those organisms which are not considered to be a GMO[49].

With the Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Amendment Regulations enacted in 2016 a new provision (Section 3 (1) (ba)) was inserted to clarify which mutagenic treatments do not result in the generation of a GMO. The clarification exempts "organisms that result from mutagenesis that uses chemical or radiation treatments that were in use on or before 29 July 1998". That exemption replaces the respective reference in the 1998 version of the Regulations relating to "chemical or radiation treatments that cause changes in chromosome number or cause chromosome rearrangements".

The 2016 amendment was enacted in accordance with a ruling by the High Court of New Zealand on a dispute concerning the regulatory status of organisms modified by ZFN-1 and TALENs. As discussed in the following chapter the court ruling clarified the regulatory status of the disputed applications.

This ruling dismissed a prior decision on the regulatory status of ZFN and TALEN applications (SDN-1) made by the NZ-EPA under its processes, and led to the introduction of the above mentioned legal clarification. It also defined the list included in the Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations 1998 as a closed list (EPA 2016, KERSHEN 2015).

Involved authorities

Two authorities are involved in approval and regulation, the New Zealand Environmental Protection Authority (NZL-EPA) and Food Standards Australia New Zealand (FSANZ). While

[49] "(1) For the purposes of the Act, the following organisms are not to be regarded as genetically modified:

(a) organisms that result solely from selection or natural regeneration, hand pollination, or other managed, controlled pollination:

(b) organisms that are regenerated from organs, tissues, or cell culture, including those produced through selection and propagation of somaclonal variants, embryo rescue, and cell fusion (including protoplast fusion):

(ba) organisms that result from mutagenesis that uses chemical or radiation treatments that were in use on or before 29 July 1998:

(c) organisms that result solely from artificial insemination, superovulation, embryo transfer, or embryo splitting:

(d) organisms modified solely by (i) the movement of nucleic acids using physiological processes, including conjugation, transduction, and transformation; and (ii) plasmid loss or spontaneous deletion:

(e) organisms resulting from spontaneous deletions, rearrangements, and amplifications within a single genome, including its extrachromosomal elements.

(2) Despite anything in subclause (1)(d), if nucleic acid molecules produced using in vitro manipulation are transferred using any of the techniques referred to in subparagraph (i) or subparagraph (ii) of subclause (1)(d), the resulting organism is a genetically modified organism for the purposes of the Act"

FSANZ[50] is responsible for food and feed safety, NZL-EPA deals with environmental release of new organisms, including GMOs.

Regulatory approach

The use of new organisms needs approval by NZ-EPA. According to Section 26 of the HSNO Act, the NZ-EPA may determine, in response to an application, whether an organism is a "new organism" and thus covered by regulation. The respective decision has to be published. However the above noted court ruling clarified that NZ-EPA does not have the mandate to broaden or narrow the scope of the act by its interpretation of the act or the regulations (KERSHEN 2015).

The definition of GMOs (as one class of new organisms) is provided in the HSNO Act in Part 1, Section 2 and is based on a process-oriented trigger. This general definition refers to any genetic modification by in vitro techniques and includes also the genetically modified progenies of the regulated GMOs in the scope of the legislation[51].

The definition was further clarified by the Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations which lists types of organisms which are not considered as GMOs (among others organisms that result from mutagenesis by chemical or radiation treatments).

Crops and plants which are not regulated under the HSNO Act are subject to general regulations, including the requirements for variety registration according to the NZ Seed Varietal Certification Scheme. The scheme is implemented as a non-statutory seed certification system which is overseen by the Ministry of Primary Industries (MPI). Growers must observe the standards and procedures published by MPI as Appendix 1, Seed Field Production Standards[52]. Imported seed and plant material is also subject to the NZ requirements for biosecurity (see below).

3.9.2 Coverage of nGMs by the NZL regulatory framework

In 2013, after receiving an application, the NZ-EPA concluded that SDN-1 using ZFN and TALEN are not GMOs and therefore new organisms under the Act (KERSHEN 2015). This decision was appealed to the High Court of New Zealand, which ruled that the techniques meet the definition of a GMO and that the EPA is not allowed to expand the list of exempted organisms in the Hazardous Substances and New Organisms (Organisms Not Genetically Modified) Regulations (SUSTAINABILITY COUNCIL OF NEW ZEALAND 2017).

Subsequently the regulation was amended in 2016 to make clear that only organisms resulting from mutagenesis that uses chemical or radiation treatments are not considered GMOs. In addition the government decided that all new techniques should be regulated as GMOs and therefore fall within the scope of the HSNO Act (SMITH 2016, SUSTAINABILITY

[50] Information in relation to FSANZ and its work is provided in detail in chapter 3.8.1

[51] "genetically modified organism means, unless expressly provided otherwise by regulations, any organism in which any of the genes or other genetic material— (a) have been modified by in vitro techniques; or (b) are inherited or otherwise derived, through any number of replications, from any genes or other genetic material which has been modified by in vitro techniques."

[52] http://www.mpi.govt.nz/document-vault/115

COUNCIL OF NEW ZEALAND 2017). It should be noted that Australia and New Zealand implement different definitions to regulate the environmental release of genetically modified organisms, set out under the Australian GTA and the HSNO Act, respectively. For labelling purposes of GM foods both countries use a similar approach, under the joint (Trans-Tasman) regulatory regime based on a definition of covered products by FSANZ.

As described in chapter 3.8 for Australia, products considered as being non-GM are not automatically covered by the Novel Foods Standard.

The approach of FSANZ to address the regulatory challenges presented by nGMs in a series is also outlined in chapter 3.8.2.

3.9.3 **Risk assessment requirements for GMOs and nGM applications**

The Hazardous Substances and New Organisms Act requires that applications include information on the adverse effects of the new organisms.

For all applications the following minimum standards have to be observed (HSNO Act, Section 36): New organisms cannot be authorised if it is likely that they cause

- any significant displacement of any native species within its natural habitat; or
- any significant deterioration of natural habitats; or
- any significant adverse effects on human health and safety; or
- any significant adverse effect to New Zealand's inherent genetic diversity; or
- disease, be parasitic, or become a vector for human, animal, or plant disease, unless the purpose of that importation or release is to import or release an organism to cause disease, be a parasite, or a vector for disease.

Furthermore NZ-EPA needs to consider the following issues in their decision, namely

- the ability of the organism to establish an undesirable self-sustaining population; and
- the ease with which the organism could be eradicated if it established an undesirable self-sustaining population.

The New Organisms unit within NZ-EPA is responsible to conduct a risk assessment addressing the above considerations and for managing potential risks from new organisms. Guidance for the risk assessment of New Organisms according to Part 5 of the HSNO Act is provided by the Hazardous Substances and New Organisms (Methodology) Order first published in 1998 and amended in July 2011[53].

The methodology outlined in this order must be consistently applied by NZ-EPA for decision making. The order specifies the role of the Authority and of advisory committees and includes provisions concerning the information which may be used by the authority when considering an application including any relevant information submitted by the public, the evaluation of costs and benefits associated with the application and the consideration of scientific or technical uncertainties associated with assessments during decision making.

[53] Hazardous Substances and New Organisms (Methodology) Order 1998 (SR 1998/217): http://www.legislation.govt.nz/regulation/public/1998/0217/4.0/DLM254556.html

According to an amendment of the HSNO Act in 2005 NZ-EPA may authorise conditional releases of new organisms (HSNO Act, Section 38A), which may otherwise not be authorised without controls or further risk management measures. Such conditional approvals are time limited; they typically expire after 5 years unless otherwise specified by NZ-EPA (HSNO Act, Section 38E). According to this procedure NZ-EPA can require specific risk management measures which may also include monitoring determined in a case by case manner. The authority therefore recommends to be consulted before an application is filed for guidance regarding risk management issues that need to be addressed[54].

To grant conditional releases of new organisms the assessment of an application needs to indicate that the application will meet the minimum standards outlined above if the mandated risk management measures are observed (HSNO Act, Section 38A)[55].

Any organisation or member of the public can make submissions on applications while they are evaluated by the authority. The issues addressed in these submissions are considered as an input to the decision making for an application[56].

nGM applications are regulated according to the HSNO Act and no specific regulations are implemented.

In addition to the HSNO Act requirements, a strict regime for biosecurity is implemented by NZ. A biosecurity clearance is required for imported organisms in order to demonstrate their conformity to the national health standards. Since all imported organisms are regulated, nGM crops would also be subject to general biosecurity requirements under that regime, even if they are not considered to be GMO. The Biosecurity Division of the MPI is responsible for the implementation of the biosecurity requirements.

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[54] http://www.epa.govt.nz/new-organisms/about/Pages/Who-is-the-New-Organisms-team.aspx

[55] According to HSNO Act, Section 38K the controls that the Authority may impose on a conditional release approval may include but are not limited to

(a) controlling the extent and purposes for which organisms could be used:

(b) requiring any monitoring, auditing, reporting, and record-keeping:

(c) imposing any obligation to comply with relevant codes of practice or standards (for example, to meet particular co-existence requirements):

(d) requiring contingency plans to be developed to manage potential incidents:

(e) limiting the dissemination or persistence of the organism or its genetic material in the environment:

(f) requiring the disposal of any organisms or genetic material:

(g) limiting the proximity of the organism to other organisms, including those that could be at risk from the conditionally released organism:

(h) setting requirements that must be met for any material derived from the organism:

(i) imposing obligations on the user of an approval, including levels of training or knowledge, limits on the numbers of users who may hold an approval, and the persons that they could deal with in respect of the organism:

(j) specifying the duration of the approval or of a control before requiring review by the Authority, and the nature of that review.

[56] https://www.epa.govt.nz/public-consultations/

Imported seeds or plant material for cultivation needs to comply with the respective import health standard (IHS 155.02.05) issued under section 24A of the Biosecurity Act 1993[57]. The procedure involves submission of specific documentation, checking the biosecurity status of the respective species and it may involve assessment under guidance of the MPI and quarantine procedures upon entry. NZ-EPA is responsible for the assessment and approval of new organisms (as defined under HSNO), which are not already covered by the biosecurity system.

3.9.4 Outstanding aspects of the existing regulatory framework in New Zealand

- New organisms (incl. GMOs) are regulated by the HSNO-Act (which also addresses hazardous chemical substances with separate requirements). In addition GM food safety is in the responsibility of FSANZ, a binational Australian/New Zealand authority.
- Definitions of the trigger implemented in the HSNO act refer to the use of in vitro technologies in a general way, therefore the interpretation by the competent authority matters significantly.
- A court ruling addressing certain SDN-1 genome editing applications established that NZ-EPA may not change the scope of the act by their decision-making. Following the ruling the government decided that all nGM approaches should be subject to regulation – only classical mutagenesis was exempted by an amendment in 2016.
- Like in Australia risk assessment requirements for GMOs and regulated nGM plants are similar.

3.10 South Africa

3.10.1 Main features of the South African regulatory framework

Existing legislation

The regulation of GMO in South Africa is dated back to 1979 when the first regulatory body, the SAGENE (South African Committee on Genetic Experimentation) was established. In addition to developing guidelines for the assessment of GMOs, SAGENE also served as an advisory body for the government on legislation and import of GMOs.

The GMO act was adopted in 1997 and amended in 2006 (GMO-ACT 1997). The aim of the GMO act is to promote the responsible development, production, use and application of GMOs, but also to protect humans and the environment for adverse effects. Besides a risk assessment related to these latter aspects, socio-economic aspects can also be considered. The act also establishes the responsible authorities and lays down the authorization procedure, which follows to a large extent the requirements laid down in the CPB.

Authorities involved in the authorisation process

The main competent authority for authorizing GMOs is Department of Agriculture, Forestry & Fisheries (DAFF). The Act prescribes the following structures:

[57] https://www.mpi.govt.nz/importing/plants/seeds-for-sowing/requirements/

- The Executive Council (EC), the decision-making body that consists of eight members representing seven different state agencies, i.e. DAFF, Department of Health (DoH), DST, Department of Environmental Affairs (DEA), Department of Trade & Industry (the DTI), Department of Labour (DoL) and Department of Water Affairs (DWA), together with the chair of the Advisory Committee.
- The Advisory Committee (AC), a panel of independent scientists that evaluates all applications.
- The Registrar (seated within the DAFF), responsible for administering the Act.
- Inspectors, responsible for ensuring adherence to permit conditions.
- The DEA may invoke an environmental risk assessment if certain criteria are met (see below Chapter 3.10.3).

Regulatory approach

The GMO Act of 1997 (Article 1) provides the following definition for GMOs which are covered by the act: "*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*", which is very close to the wording used in Directive 2001/18/EC. As this is the basis for the regulation, the applicability of the legislation is defined by the way in which organisms are produced, i.e. how new traits are introduced. Therefore the definition implemented in the SA regulation framework is considered to be process-oriented.

3.10.2 Coverage of nGMs by the South African regulatory framework

No official statement on how to classify nGM applications has been published by the competent authorities of South Africa. However, the report published by the ASSAF (ACADEMY OF SCIENCE OF SOUTH AFRICA 2017) provides some insights into the discussions, at least from the point of view of the ASSAF.

In this report the ASSAF states that the current GMO legislation is based on a process oriented approach regarding the trigger for regulation. The ASSAF also concludes that, though in its opinion a product oriented approach would be more suitable, "*South Africa's current regulatory framework for GMOs could therefore, with only minor updates to the GMO Act's Regulations and guidelines, be used to effectively regulate NBTs and all possible future genome modifying techniques*" (ACADEMY OF SCIENCE OF SOUTH AFRICA 2017). In addition, crops developed by nGM are subject to regulatory requirements with regard to variety approval according to the Plant Improvement Act (PIA), 1976 (Act No 53 of 1976), Sec. 13(2) and regulations, which do apply for new crops to be introduced into South Africa, e.g. provisions for importation of propagating material according to PIA, Sec. 26(2) and phytosanitary clearance according to the respective provisions of the Agricultural Pests Act, 1983 (Act No. 36 of 1983).

The aforementioned provisions of the PIA are only applicable to plant species specifically listed in the respective guidelines (DAFF, Guidelines and procedures for the importation of

unlisted varieties in terms of the PIA[58]) and exclude plants introduced for ornamental purposes. The purpose of PIA is to ensure that minimum quality requirements for plants, seeds and propagating material are met, i.e. absence of weed material, pathogens or animal plant pests, trueness to variety characteristics, normal growth and germination ability (cf. Regulations relating to establishments, varieties, plants and propagating material[59]).

According to the Agricultural Pests Act and the Plant Health and Phytosanitary Policy (DAFF 2014)[60] a pest risk analysis (PRA) according to respective IPPC standards should be conducted for all imported plants. In addition health impacts to animals from toxic plants and from plants expressing narcotic substances are considered.

3.10.3 **Risk assessment requirements for GMOs and nGM applications**

Risk assessment requirements for GMOs

An environmental risk assessment for all GMOs as defined by the GMO-Act (see chapter 3.10.1) is required before authorisation to release it into the environment may be granted. GM plants which contain stacked traits resulting from either intentional intraspecific or interspecific crosses between GMOs already authorised for commercial release will still require comprehensive risk assessments. Risk assessments have been carried out for different crops (cotton, maize, and soybeans) and usually led to an approval of the respective GMO.

The requirements for risk assessment are laid down in the GMO Regulations issued in 2010, however in a very general way without giving any specifics concerning the required data or parameters to be investigated. However, further detail is provided in the guideline documents available on the DAFF website[61]. Protection goals relating to GMOs are also included in the National Environmental Management Act (NEMA) of 1998, Chapter 1, Section 4 and the National Environmental Management: Biodiversity Act (NEMBA) of 2004, Chapter 5, Section 78. The GMO Act's objective is to "… *[provide] for adequate level of protection during all activities involving GMOs that may have adverse impacts on the conservation and sustainable use of biological diversity, human and animal health*". NEMBA provides for the management and protection of the country's biodiversity, protection of species and ecosystem in need of protection.

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[58] Guidelines and procedures for the importation of unlisted varieties in terms of the PIA, 1976: http://www.nda.agric.za/doaDev/sideMenu/plantProduction/doc/GUIDELINES%20IMPORT%20UNLISTED%20VARIETIES_seed%20_PIA__Dec%202014.pdf

[59] Regulations relating to establishments, varieties, plants and propagating material: https://www.ecolex.org/details/legislation/regulations-relating-to-establishments-varieties-plants-and-propagating-material-lex-faoc073502/

[60] Plant Health (Phytosanitary) Policy for South Africa, May 2014: http://www.nda.agric.za/doaDev/sideMenu/plantHealth/docs/Plant%20Health%20(Phytosanitary)%20Policy%20Gazetted%20for%20Implimantation.pdf

[61] http://www.daff.gov.za/

Guidance for the risk assessment is provided by the DEAT (Environmental Risk Assessment Framework for Genetically Modified Organisms: A Guidance Document)[62].

The National Environmental Management Act, 1998 (Act No. 107 of 1998) establishes principles for decision making on matters affecting the environment. Section 2 of NEMA sets out the national environmental management principles, with the aim of ensuring that all activities are conducted in a sustainable manner. The release of GMOs into the environment is a listed activity in terms of the Environmental Impact Assessment (EIA) Regulations. Any GMO activities that may trigger an EIA would have to comply with section 24 (5) of NEMA, which lays down minimum requirements to be satisfied in an EIA process. This requires that risk assessment and risk management procedures be undertaken prior to the approval of any proposed activity with GMO's in accordance with the provisions of the GMO Act.

An EIA may be evoked by the Minister of DEAT in consultation with scientific experts when specific criteria apply:

- A GM in question results in changes in conventional use, e.g. pharmaceuticals in plants, biofuel production.
- A GM results in substantial changes in current agricultural practices and pest (medical, veterinary, agricultural) management practices, e.g. expansion into new agricultural areas.
- For GMOs for which there is prior evidence of changes in the agro-ecosystem dynamics that may lead to substantial changes in current agricultural practice, such as evidence of secondary pest emergence or evidence of resistance development.
- A potential negative may impact on threatened or protected organisms listed in terms of the National Environmental Management: Biodiversity Act (NEMBA).
- For releases of indigenous GM organisms.
- For GMOs with cultural geopolitical significance, or potentially negative socio-economic impact.
- For GMOs that have wild indigenous relatives.
- For GMOs that have non-indigenous weedy relatives.
- For GMOs that have the potential to become invasive.
- For the release of modified microorganisms that are expected to have a significant negative effect on the environment.
- For environmental release applications of GMOs which may be used for bio-terrorism.

The requirements for environmental impact assessment are laid down in the National Environmental Management Act:

- Identifying impacts of GMOs and their products on the environment; defining level and frequency of such impacts.

[62] ERA for GMOs: a guidance document: http://biosafety.org.za/cms/modules/media/scripts/documents/document.handler.php?media_files_id=868

- Evaluating the mode of impact.
- Analysing environmental elements and identifying them for evaluation and protection objectives.
- Description of environmental impact assessment results according to studies and analyses.
- Comparing and analysing socio-economic and environmental benefits of various protection measures.
- Proposing impact prevention or mitigation measures.

Risk assessment requirements for nGM applications

The ASSAF also deals with probable implications for risk assessment of organisms produced by nGMs, and also refers to the requirements laid down for GMOs. The report (ACADEMY OF SCIENCE OF SOUTH AFRICA 2017) analyses the existing framework and the basic principles used with regard to the applicability for nGMs. In conclusion the ASSAF states in its report:

"*GMO risk assessment has evolved over more than three decades into a robust framework that can be applied to any genetically engineered organism, irrespective of the techniques used as long as the principles of a case-by-case, comparative risk assessment apply*."

3.10.4 Outstanding aspects of the existing South African regulatory framework

- The regulatory framework provided by the GMO act is based on the CPB and influenced by the EU legislation for GMOs. The assessment approach for regulated products and the regulatory requirements for covered products implemented in South Africa are comparable to the respective provisions of the EU framework.
- The GMO act is based on a process-oriented trigger definition which comparable to the definition for GMOs used in the EU. An interpretation of the trigger regarding nGM applications was not yet provided, however the South African Academy of Sciences notes that many nGM applications would probably be covered.
- The risk assessment for GMOs and nGM applications is designed in a similar way; regulated nGMs may also be subject to an optional assessment of their socio-economic impacts.
- General agricultural, environmental and food laws are also applicable to applications not regulated by the GMO act; however focus and depth of assessment according to these laws are not comparable to requirements according to the GMO law.

4 Comparison of studied regulatory frameworks

Our study investigates the differences and similarities of regulatory frameworks for biosafety in Argentina, Australia, Brazil, Canada, the EU, New Zealand, Norway, South Africa, Switzerland, and the USA. In particular we examine how nGM applications are covered and regulated by these frameworks, including the general requirements for risk assessment. Furthermore we analyse current reviews of these systems and proposed amendments, in particular those which are developed to better address nGM applications.

Our comparison of the different frameworks is based on literature analysing and explaining the existing legislation related to regulation of biotechnology products in general and nGM applications in particular. To update and complement this information we conducted interviews with regulators and/or experts involved in risk assessment according to existing biosafety legislation. The interview partners answered our questions in a personal capacity based on the understanding that no transcripts of the interviews would be published and that no direct quotes from the interviews would be attributed to specific persons. The information from the interviews provided a background as of September 2017 against which previously published information was checked for correctness and validity. Dependent on availability and awareness further relevant literature on subsequent developments and issues pertinent to the analysed topics was included.

Contrary to previous analyses (ACADEMY OF SCIENCE OF SOUTH AFRICA 2017, NAS 2016, SCHUTTELAAR 2015, SPRINK et al. 2016b) we did not specifically focus on the regulatory status of emerging nGM applications (i.e. whether specific nGM applications are subject to a particular biosafety legislation framework or not), but on the experience with existing regulatory approaches and their procedures for risk assessment as well as on possible implications for nGM applications.

The studied biosafety frameworks are embedded in different legislative environments and all of the respective countries have actively been implementing these regulations for many years. The USA, Canada, Argentina, Brazil, and Australia are among the main producers and exporters of agricultural GM products (ISAAA 2016). In all of the selected countries an active discussion on how to deal with future regulation of nGM applications is underway at the national level.

4.1 Main features of the regulatory frameworks

All countries described in chapter 3 implemented specific requirements for the regulation of agricultural biotechnology. These frameworks share some common features, notably the intention of regulatory oversight, i.e. to ensure health and environmental safety, and the requirement for risk assessment of regulated products, e.g. modified plants, animals or microorganisms for environmental release or the use of modified food and feed products (MCHUGHEN 2016).

However, the adopted national approaches also show some marked differences regarding legislative and administrative features, scope of regulated products and the implementation of the regulatory framework.

An overview of the main features of the respective regulations frameworks is presented in Table 2. The respective situation at the EU level is included for comparison. Classification of the used regulatory trigger is according to the assessment in the study at hands.

Table 2: Regulatory frameworks for biotechnology analysed in this study - Legal foundations, characteristics and regulatory requirements for unconfined release e.g. for commercial cultivation or the marketing of regulated biotechnology products)

Country	**Main biosafety legislation**	**Framework or specific law (for env. release)**	**Regulatory trigger***	**Regulatory requirements for unconfined environmental release**	**Authorisation period (for marketing)**
European Union	Biosafety Directives and Regulations (food/feed, env. release) (1990, updated 2001/2003)	Dir 2001/18/EC, supplemented by implementing regulations and GM food and feed regulation (2003)	Process-oriented**	Risk assessment, risk management, coexistence, monitoring, labelling, detection methods	10 years, renewable
Argentina	Regulation Framework for Agricultural Biotechnology (1991)	Supplementary Resolution for release of GMOs	Process-oriented	Risk assessment, socio economic considerations	Not limited (possibility of revocation)
Australia	Gene Technology Act (2000), Food Standards Australia New Zealand Act (1991)	Supplementary Regulations e.g. Gene Technology Regulation (2001)	Process-oriented	Risk assessment, risk management and monitoring	Not limited (possibility of revocation)
Brazil	Biosafety law (1995; updated 2005)	Biosafety Law supplemented by implementing Resolutions	Process-oriented	Risk assessment, coexistence, monitoring, labelling, optional socio economic considerations	Not limited (possibility of revocation)
Canada	Regulatory Framework for Biotechnology (1993)	Framework includes regulations for plants with novel traits and novel foods and feeds	Product-oriented (novelty- and risk-based)	Risk assessment, stewardship (risk management)	Not limited (possibility of revocation)
Norway	Gene Technology Act (1993)	Regulations for risk assessment	Process-oriented	Risk assessment, risk management, monitoring, labelling, detection methods, socio-economic/sustainability assessment	10 years, renewable
New Zealand	Hazardous Substances and New Organisms Act (1996), Food Standards Australia New	Supplementary Regulations (1998, 2003) and Methodology Order (1998)	Process-oriented	Risk assessment, risk management, monitoring (for conditional releases)	Not limited (possibility of revocation)

	Zealand Act (1991)				
South Africa	GMO Act (1997)	GMO Regulations (amended in 2010)	Process-oriented	Risk assessment, monitoring, labelling, detection methods, optional socio economic considerations	Not limited (possibility of revocation)
Switzerland	Gene Technology Act (2003)	Release Ordinance (2008)	Process-oriented	Risk assessment, monitoring, labelling, detection methods	10 years, renewable
USA	Coordinated framework for the regulation of biotechnology (1986)	Framework refers to relevant sectoral legislation (e.g. Plant Protection Act, Federal Insecticide, Fungicide, and Rodenticide Act, Toxic Substances Control Act)	Product-oriented (risk-based)	Risk assessment	Not limited (possibility of revocation)

***** Classification of the regulatory triggers is not based on legal determination, but according to an assessment by the authors, based on information in the literature and information gathered from interviews with regulatory experts.

** Classification is disputed, some sources claim that the trigger is both process- and product-oriented (BVL 2015, KAHRMANN et al. 2017).

4.1.1 **Regulatory approaches**

The comparison of the different analysed regulatory frameworks indicates that there are differences regarding the following aspects:

- Time of entry into force
- Pursued regulatory approach: adaptation of existing laws vs. new sectoral legislation
- Type of regulatory trigger (e.g. process-oriented vs. product-oriented triggers)

All of the analysed regulatory frameworks for biotechnology were devised and/or implemented prior to the CPB coming into force in 2003. However compatibility with the CPB is not an issue for all countries included in the study. The USA, Australia, Argentina and Canada are not parties to the Protocol. However Canada and Argentina were among the signatories of the CPB and all countries participate in the information exchange mechanism of the CPB, the BCH. All other countries included in this study and the EU are parties to the CPB and their legislation was either compatible with the CPB or respective changes were introduced to increase compatibility, e.g. in Brazil.

Some countries, including e.g. the USA, Canada, Argentina, Norway and the EU, implemented a framework for agricultural biotechnology very early (prior to 1990 or in the early 1990ies) to respond to the need for specific legislation to address the agricultural use of GM products for field testing as well as for unconfined environmental release, e.g. for

commercial cultivation of GM crops. However the analysis shows that the respective legislations are based on different approaches.

It is noteworthy that in all regulatory frameworks analysed in this study the regulated entities are the products (organisms) which were generated by biotechnological methods and not the methods itself. Also the risk assessment which needs to be conducted is addressing the characteristics of the product (organisms) rather than being focused on methodological aspects.

Most of the countries and the EU chose to establish new sectoral legislation for applications of biotechnology, including the agricultural use of GMOs. This resulted in adoption of biosafety laws or gene technology acts supplemented by specific regulations for implementation in the EU and in Norway, Switzerland, Argentina, Brazil, Australia, New Zealand, and South Africa. The respective pieces of legislation set the scope of the regulations and contain definitions of products or organisms which are subject to the respective legislation. Since the focus of these biosafety regulations was on applications of GM technology the adopted definitions are considered by regulators and stakeholders as well as studies published on this topic to be mostly process-oriented.

New Zealand stands out from the mentioned group of legislatures since it adopted sectoral legislation which addresses different regulated products or organisms (the HSNO act). The scope of the HSNO act comprises hazardous chemical substances as well as organisms new to New Zealand, including GMOs. However both areas of regulation are treated independently by the authority regarding the specific regulatory procedures, risk assessment requirements, etc.

The USA and Canada chose to use and update existing legislation to establish their regulatory frameworks for biotechnology applications. These countries also chose to implement product-oriented triggers for the respective regulatory requirements, e.g. for authorisation of use and for risk assessment of regulated products or organisms. However different regulatory triggers were adopted in the USA and Canada.

The different regulatory agencies in the USA use triggers based on certain product characteristics, which are considered to be risk-related: e.g. plant pathogenicity, weediness of parental plants, pesticidal effects of the new traits (e.g. in PIPs). However the plant pathogenicity trigger also captured products developed by using DNA sequences derived from plant pathogens (like promoter and terminator sequences from Agrobacterium and plant viruses) and all GM plants developed by *Agrobacterium*-mediated transformation. Since both the introduced sequence-elements as well as the transformation method will not result in pathogenic products, this trigger is considered to be related to aspects of process rather than product (McHUGHEN 2016).

Canada on the other hand implemented a regulatory trigger based on the novelty of the respective products in combination with a given plausibility that these products may exhibit adverse (environmental) effects. Canada thus regulates all novel plants irrespective of the technology used for their production. The scope of the Canadian regulations also comprises novel plants derived by conventional breeding methods like classical mutagenesis e.g. crop plants with a novel trait resulting in resistance to (broadband) herbicides. In contrast such plants would only be subject to the USA framework if the HR trait is associated with a

specific risk factor as mentioned above. In the other analysed countries such plants derived by conventional breeding methods are not subject to the respective biosafety laws.

4.1.2 **Requirements according to the different biosafety frameworks**

Table 2 also indicates that the regulatory requirements according to the analysed legal frameworks are quite different and lists examples of such requirements which apply in the respective frameworks in addition to a mandatory risk assessment. Such additional requirements mandated by certain regulatory frameworks are:

- Risk management
- Coexistence
- Monitoring
- Labelling
- Detection method
- Socio-economic assessment

Risk management measures are typically implemented for field-trials of regulated organisms in all analysed regulatory frameworks. Some of these frameworks (e.g. Europe and Canada) may also implement case-specific risk management requirements (e.g. stewardship or risk management measures to counter the development of pests resistant to the pesticidal traits). Risk management obligations may also be imposed in New Zealand for conditional releases of new organisms according to HSNO Act (HSNO, Section 38A).

Specific coexistence measures to ensure that biotech crops do not impact the cultivation of non-biotech crops are mandated only by the regulatory frameworks of the EU, Norway and Brazil. In other countries only non-legally binding (stewardship) programs are implemented and general rules concerning neighbourhood-rights and sectoral requirements for coexistence, e.g. for the application of plant-protection products are in place.

Monitoring is required by several countries; however the implemented approaches are quite different regarding time-frames and measures. Comprehensive monitoring of unconfined releases based on case-specific monitoring, which addresses identified risks and general surveillance to detect unintended effects, is only implemented in European countries and South Africa. Brazil is requiring that alert systems for notifications of potential adverse effects by users of the authorised products are established. Australia only implements case-specific monitoring for certain unconfined release applications. The other regulatory frameworks implement monitoring only for confined release applications.

Labelling of regulated products for information of the consumer (buyer of products) is required by the European countries, as well as Brazil.

The requirement to provide a suitable detection method for a specific product is usually connected to a labelling-regime to provide a means to ensure analytical detection for inspection and traceability purposes. The EU, Norway, and Switzerland require submission of such a detection method by the applicant. Until recently Canada had implemented such a requirement, however this was not connected to a labelling requirement and was abandoned recently (CFIA pers. comm.).

Several regulatory frameworks contain provisions that socio-economic considerations need to be conducted (Norway), or may be conducted depending on respective decisions by the authorities (Brazil, South Africa).

The EU framework and the closely related regulatory frameworks of Norway and Switzerland foresee that the consent for the authorisation is time-limited (for a period of 10 years). However, product authorisations may be renewed by submitting a renewal notification prior to expiration. Renewal of authorisation is subject to a re-assessment of the product, with a focus on new information available for the product and information gathered by monitoring during the prior authorisation period. In all other frameworks product consent is not time-limited and authorisations do not expire unless they are revoked by the authority.

4.1.3 **Review of existing legislation**

A number of countries are or were reviewing their policies and/or regulations, either due to emerging needs, e.g. associated with challenges due to new technologies like the nGMs covered in this study (technical reviews Australia, Brazil, South Africa, Switzerland) or to address accumulated experience with the existing regulatory frameworks. Such general policy reviews are ongoing in the USA and in Australia (FEDERAL REGISTER 2017, LGFGT 2018). However all countries are actively discussing how to deal with nGM applications. Australia has conducted a technical review of its GTR 2001 and has implemented a technical update concerning the regulation of a number of specific nGMs, such as genome editing applications, RNAi methods and null-segregant approaches, while a general broader policy review is under way.

The USA and Canada are also reviewing the current risk assessment requirements, which may result in fewer information requirements for some types of applications, e.g. GMOs harbouring similar traits as already authorised products or certain nGM applications (CFIA pers. comm.). Other countries including Switzerland and Norway are also discussing possible amendments of the existing risk assessment approaches.

4.1.4 **Involved authorities and distribution of responsibilities**

An important issue for implementation of a specific regulatory framework is how specific responsibilities for assessment as well as decision making are placed with the involved authorities and institutions. The different approaches to regulation chosen in the different frameworks are also reflected in the respective distribution of responsibilities between the involved authorities as indicated in Table 3.

It is noteworthy that some regulatory systems place the responsibilities for decision making, risk management and the responsibility for risk assessment with separate authorities: examples for such a separation are the EU, Norway, Argentina, Brazil, and South Africa. In the other frameworks a single authority is responsible for both decision making and risk management; however the specific work is taken care of by different departments in the involved institutions.

In countries where many different considerations, e.g. on socio-economic effects, on compatibility with overall policies and on ethics, need to be taken into consideration usually additional institutions are involved to provide technical support. This is considered to

strengthen the interdisciplinary cooperation between different institutions and to enhance the societal robustness of decisions (Norwegian Ministry of Environment, pers. comm.). However this is associated with the issue that overall decision making is more difficult when considerations addressing different aspects have to be combined appropriately into an overall decision.

In the regulatory frameworks, which implement a product-oriented trigger (USA, Canada) existing statutory agencies regulate products developed by biotechnological methods as well as comparable non-biotech products.

Regarding product authorisations some regulatory frameworks place the responsibility for decisions for different scopes of use (e.g. environmental release and cultivation or food and feed use) with different authorities. Such split responsibilities are implemented e.g. in the USA, Canada, Australia and New Zealand. In such situations proper coordination is required, which may be provided by a lead institution, e.g. CFIA in Canada, or which is practised as a feature of the implemented regulation framework, e.g. in the USA.

Table 3 Authorities involved in the implementation of the regulatory framework

For Abbreviations pls. see: List of Abbreviations (page 8)

Country	**Entity responsibe for determination of the regulatory status of appl.**	**Lead Authority (env. release applications)**	**Shared responsibilities**	**Other national institutions involved in authorisation**
European Union	Member states´ competent authorities	Food/feed (incl. cultivation): EFSA (RA), Decision by member states based on proposals by the European Commission	Field trials and contained use: Member states responsibility	RA of cultivation applications: Member states competent authorities supported by other natl. institutions
Norway	Ministry of Environment	Ministry of Environment		Ministry of Health Care Services, DIRNAT
Switzerland	FOEN (natl. env. agency)	FOEN		FOPH (food and biocidal products), Swissmedic (medicines), FSVO (veterinary medicines), FOAG (seeds, feeds, fertilisers, pesticides)
USA	USDA/APHIS (Plant health unit, Dept. Agriculture)	USDA/APHIS	US-EPA (traits expressing pesticides) FDA (food & feed)	-
Canada	Respective statutory authority (agriculture, health,	CFIA	HC (food & feed applications) EC	PMRA (pest control products) FOC (fish products)

	env.); CFIA , HC and EC coordinate decisions		(microorganisms)	
Argentina	Ministry of Agriculture, Livestock and Fisheries based on a CONABIA opinion	Ministry of Agriculture, Livestock and Fisheries	-	CONABIA, SENASA, DNMA
Brazil	MAPA (Min. Agricult.); technical support by CTNBio	MAPA	-	CTNBio (RA), MoH, MoE, CNBS
Australia	OGTR (based on government policies)	OGTR	-	FSANZ, APVMA, TGA, DAFF, NICNAS, MoE
New **Zealand**	NZ-EPA based on government policies	NZ-EPA	FSANZ (food & feed)	-
South Africa	DAFF (Dept. Agriculture, Fisheries)	DAFF	DEAT decides on environmental risk assessment	Executive Council: DAFF, DoH, DEAT, DTI, DoL, DAC

4.1.5 **Determination of regulatory status**

To determine which specific products fall under a certain regulation is an important step in all regulatory frameworks. All frameworks therefore contain specific legal triggers, e.g. definitions of regulated articles, to facilitate the determination of the regulatory status of a specific organisms or product.

However not all regulatory frameworks addressed in this study explicitly assign statutory responsibilities to specific authorities to determine the regulatory status of applications nor do all frameworks outline specific procedures which need to be followed for this determination. In those cases it is assumed that the definitions provided in the legislation are sufficiently clear to enable developers to decide whether a specific application is regulated and to submit respective notifications for authorisation.

In case of doubts the developers of specific products can consult with the competent authorities concerning the regulatory status of the products. Some authorities, e.g. OGTR in Australia and CFIA in Canada, even actively recommend that developers address any unclear issues during pre-submission consultations. Authorities like OGTR can only provide advice to developers and offer an opinion concerning the regulatory status of specific applications, but have no statutory authority to issue formal decisions on this matter. Typically consensus between developers and authorities is reached by way of pre-submission consultations and the respective opinions of the OGTR were never challenged by developers.

In some countries, developers have requested declaratory decisions on the regulatory status of specific nGM applications from the competent authorities, e.g. in of some EU member states, including Germany, Sweden and the UK. These authorities have made decisions on the regulatory status of herbicide-resistant crops developed by ODM at the national level in the present absence of a respective EU-level policy (KAHRMANN et al. 2017, SPRINK et al.

2016a). Until the ruling of the ECJ with regard to Case C-528/16 was delivered the European Commission did not repeal these national decisions nor adopted a harmonised EU-level policy towards the status of specific nGM applications.

In other countries the regulatory status of a product is determined by the respective statutory authority (e.g. Argentina, USA, Canada, New Zealand). The respective frameworks provide a mechanism for developers to obtain a regulatory decision on the status of specific products, which is based on the definitions and criteria contained in the respective legal instruments, e.g. Resolution No. 173/2015 in Argentina, the HSNO-Act in New Zealand and Title 7 CFR and the respective laws in the USA and Canada. In the latter countries different statutory authorities are responsible to determine the regulatory status under the different applicable laws, e.g. for applications of biotechnology for products for environmental release or for food and feed products. As demonstrated by the Canadian example the definitions for regulated products may differ slightly in the different implicated laws (see chapter 3.5.2). However the respective different authorities in Canada are closely coordinating their decisions to avoid unintended inconsistencies.

The respective decisions are not always published; in some countries, e.g. in Canada, only information on regulated products is shared with the public. In the USA the public is informed of all notifications and decisions of the “Am I regulated?”-process conducted by USDA-APHIS for products where the developer is not able to determine the regulatory status with confidence himself.

The results of the processes to determine the regulatory status of specific applications may also be challenged in court. In New Zealand a court ruling indicated that certain nGM-applications (ODM and GE-applications) could not be exempted from regulation by NZL-EPA without a respective policy decided by the New Zealand government (KERSHEN 2015).

In France a decision by the government to not ban the cultivation and marketing of herbicide tolerant oilseed rape varieties developed by targeted mutagenesis was recently challenged at the national courts by stakeholders from the civil society. As the French laws inferred in the complaint are transposing EU law, the French Conseil d’État referred a number of crucial issues to the ECJ for decision (Case C-528/16). Among others the ECJ addressed the question whether organisms developed by techniques to generate mutations at specific genome locations (“directed mutagenesis”) are subject to the requirements of the EU regulations for GMOs. As already indicated in the previous chapters in July 2018 the ECJ ruled that such applications are indeed GMOs according to the current definition provided in Directive 2001/18/EC and that such applications are not exempt from biosafety requirements like products of random mutagenesis (ECJ 2018).

Table 3 also indicates that the responsibility for setting the regulatory status of specific products and the responsibility for decision making on the authorisation of such products is mostly placed with similar institutions in the analysed countries.

4.2 Coverage of nGM applications by national regulatory frameworks

4.2.1 Coverage by existing biosafety regulations

An interesting question is how the different regulatory frameworks implemented in the investigated countries deal with the suite of nGM applications addressed by this report and

whether new regulations are being developed to address the resulting regulatory challenges. An overview on some aspects relating to these questions is provided in Table 4.

Table 4 Regulatory aspects related to nGM applications

(appl.: application)

Country	Current regulatory approach	Policy development regarding nGMs	Focus of policy amendments	Current experiences with nGM applications
European Union	Determination if specific types of nGMs are subject to GMO legislation	No amendment of Directive 2001/18/EC proposed by Europ. Commission yet; ECJ ruled that directed mutagenesis is subject to GMO legislation (ECJ 2018)	-	No experience on European level with applications for unconfined release and placing on the market; however field trials with some nGM appl. are conducted (SAM 2017)
Argentina	Determination if nGM product is subject to GMO legislation	Supplementary resolution adopted 2015 providing criteria for case-by-case decisions (Resolution No. 173/2015)	All types of nGMs	Until June 2018 12 requests were evaluated according to Resolution No. 173/2015, incl. 10 applications of genome editing, mostly in plants, mostly determined not regulated (OECD 2018)
Australia	Determination if nGM process is subject to GMO legislation	Australia adopted technical amendments to legislation proposed by OGTR	Genome editing (SDN-1), RNAi	No applications for unconfined release; field trials with some nGM applications are conducted
Brazil	Determination if nGM product is subject to GMO legislation	Supplementary resolution adopted in January 2018 (Normative Resolution No 16)	All types of nGMs	Use of nGMs in contained use facilities; two yeast lines modified by genome editing were evaluated according to Resolution No 16 (not regulated)
Canada	Determination if individual nGM product is novel	Review of risk assessment requirements initiated	-	Several appl. authorised (e.g. cisgenic potato, genome edited oilseed rape)
New Zealand	GMO legislation is currently applied for all nGMs	Government adopted policy to direct technical ruling by NZ-EPA, no immediate policy changes foreseen	GMO legislation only exempts chemical or radiation induced mutagenesis	Use of nGMs for research and development activities; some genome editing determined to be regulated
Norway	Determination if specific types of nGMs are subject to GMO legislation	Technical discussions to inform further steps (following EU approach)	-	No appl. for unconfined release submitted; use of nGMs in contained use facilities
South Africa	GMO legislation is currently applied for all nGMs	Discussion on policy amendment ongoing	-	No appl. for unconfined release submitted; use of nGMs in contained use facilities

Switzerland	Determination if specific types of nGMs are subject to GMO legislation	Stakeholder discussions to inform future policy	-	No appl. for unconfined release; field trials with some nGM appl. are conducted
USA	Determination if individual nGM product is regulated	Consultations on policy to deregulate certain techniques (e.g. cisgenesis)	Cisgenesis, genome editing	Several decisions to exempt nGM appl. from regulation; a number of nGM appl. in regulatory review

In general no specific regulations for nGM applications, which are independent from the existing regulatory frameworks for GMOs or Novel Plants, were adopted in the countries addressed in this study.

Countries like the USA and Canada, which implement systems based on product-oriented regulatory triggers that are mostly or fully independent from technology-related considerations are experiencing fewer challenges to apply their regulations to the emerging nGM applications than countries which implemented specifically defined process-oriented regulatory triggers in their legislation. Canada for example considers that the current PNT regulations are providing a consistent framework to also address current and emerging nGM-applications (CFIA Pers. Comm.).

Further development of such systems is not specifically driven by specific issues related to nGM applications. Rather general changes are considered based on the accumulating experience with the implementation of the existing regulatory frameworks. This might e.g. be changes to increase the overall consistency of the system (NAS 2016) and to better focus the risk assessment, taking into account the accumulated experience from previous assessments of GMOs and PNTs (SHEARER 2014; CFIA Pers. Comm.).

Authorities in both USA and Canada determine the regulatory status of specific nGM plants based on the evaluation of the individual nGM applications (i.e. an approach to decide whether a specific nGM application is covered by the respective regulatory triggers). The decision is based on information provided by the developer of the nGM plant. Both countries use the implemented pre-decision consultation mechanisms to obtain information relevant for decision-making on the regulatory status of specific nGM applications (see also Chapters 3.4.1 and 3.5.1). However the level of transparency regarding the outcomes of the proceedings is different: In the USA all submissions for the determination of the regulatory status of nGM applications as well as the decision letters of USDA are made public. In Canada information on individual products as well as on the review by authorities is only available for nGM applications which are determined to be subject to the Canadian PNT regulations.

Countries which implement process-oriented regulatory triggers are currently deliberating whether specific nGM applications or types of applications developed with a certain nGM approach are subject to the existing regulations for GMOs.

Such deliberations can either be conducted proactively in the framework of policy reviews, in order to evaluate the general appropriateness of the existing regulatory approach, like the current reviews in Australia (LGFGT 2018) or in the USA (NAS 2016). Such reviews may also be triggered by anticipated challenges to the existing regulatory system by emerging

technological development, like the review of nGMs by the respective working group of the European Commission and the EU member states (NTWG 2012) or the ongoing technical review of regulatory coverage of certain nGMs by the OGTR in Australia. These processes may involve policy makers, regulatory bodies, technical expert groups, scientific academies and a wide range of other stakeholders, e.g. during consultations of the public.

On the other hand such deliberations may also result from the situation that individual nGM applications are presented to regulators for a determination of their regulatory status. The decisions of the NZ-EPA on ODM and TALEN plants in New Zealand and a herbicide-resistant ODM oilseed rape in EU member states represent current examples for such proceedings. The authorities of most of the countries surveyed in this study are prepared to conduct such evaluations in the absence of general policy decisions on the regulatory status of nGM applications. The results of the respective legal evaluation or of any court proceedings which are initiated in response to the regulatory decisions are then of further relevance for other applications developed by similar technical approaches.

All such deliberations may result in general or technical amendments of the existing legislation, e.g. of the definitions for regulated articles. Respective national discussions are currently at different stages of progress and not concluded in most of the countries covered in this study. For some of these countries, e.g. South Africa, no information is available at the moment, if any legislative changes will be proposed, neither which specific amendments will be developed and when they will come into effect. However the survey at hands offers some indications regarding the different approaches and timelines.

Argentina and Brazil have already adopted specific legislation addressing the issue of nGM applications (Resolution No. 173/2015 in Argentina, Normative Resolution No 16 of Jan 2018 in Brazil). These resolutions are supplementing the existing regulation framework for agricultural biotechnology introduced and provide guidance regarding the procedures and the criteria for decisions made by the authorities to establish the regulatory status of individual nGM applications (LEMA 2019, WHELAN&LEMA 2015).

In New Zealand an initial court ruling addressed and uplifted a NZL-EPA decision to not regulate specific types of nGM applications (ZFN- and TALEN-mediated genome editing). Subsequently to the court decision the government introduced a clarification that only products developed by chemical or radiation induced mutagenesis are exempted from GMO legislation under the HSNO Act. A cabinet proposal for deregulation of all nGM applications, which are of similar risk as products of conventional breeding, was not further developed (SC-NZL pers. comm.). Instead the government decided, that all nGMs should be regulated as GMOs according to the current definition contained in the HSNO Act (see chapter 3.9.1).

The Academy of Sciences in South Africa prepared proposals how to deal with nGM applications. However as of mid-2018 no legal decisions have been taken on the matter.

Australia has implemented technical amendments to the existing definitions to better address nGM applications. The 2018 update of the GTRs codified a OGTR proposal that SDN-1 genome editing applications based on site-directed nuclease systems, which are not used in combination with a nucleic acid template to direct specific sequence changes or to insert additional sequences should not be regulated as GMOs. Furthermore the use of RNA-molecules to induce RNAi-effects is considered to not result in regulated applications, provided that no genetic construct or viral vector to express such RNAs is introduced into the

targeted organisms. Further amendments might be proposed in the course of the ongoing third review of the Australian regulatory framework for gene technology.

The discussions in several countries on the technical interpretation of the existing definitions for GMOs focus particularly on organisms which were modified by targeted mutagenesis by application of nGMs for genome editing, in particular by SDN-1 and SDN-2 applications and ODM. It is discussed whether such nGM organisms may be regarded similar to organisms which were generated by random mutagenesis , e.g. based on irradiation or treatment with chemical mutagens (KAHRMANN et al. 2017). At the EU-level however the ECJ ruling did not support such an approach, but rather determined that genome editing approaches are indeed subject to the existing biosafety regulations (ECJ 2018).

Another significant issue is how nGM applications based on the use of null-segregants are regulated by different legislations. Such applications generate intermediate breeding products containing transgenic modifications, which are removed by segregation during further breeding steps. As a result no transgenic modifications are present in the final breeding products. Such an approach is used for nGMs like reverse breeding, accelerated breeding and haploid induction. Several countries like the USA, Canada, Argentina, Brazil and Australia do not regulate such applications based on submissions by the notifiers providing scientific evidence that the transgenic insertions are indeed absent from the final breeding product.

4.2.2 **Coverage of nGM applications by other regulations**

nGM products which do not to fall under the provisions of the respective biosafety frameworks are still subject to other regulations addressing agricultural products (e.g. seed and plant propagating materials, animal and plant health, food and feed safety, nature conservation). Our analysis indicates that the general requirements according to such legislation in the different countries are broadly comparable. The following examples of such requirements apply to products of genome editing or other nGM applications in case it is found that these products are not subject to existing biosafety legislation:

- Variety registration regimes are implemented in all countries included in this study as well as globally to ensure seed quality, the distinctiveness and stability of traits, as well as the uniformity of seed lots and a number of safety parameters for certain plant species. These issues are assessed according to international standards (UPOV 2002).
- The general provisions of food and feed safety legislation in the different countries are also applicable to biotech products. In some countries specific products may also be covered by legislation addressing novel foods, such as Regulation (EU) 2015/2283 in the European Union.
- All of the investigated countries implement phytosanitary measures according to the WTO Sanitary and Phytosanitary (SPS)-Agreement. According to this agreement requirements for pest risk assessment can be implemented based on standards developed by the International Plant Protection Convention (IPPC), as well as weed risk assessments which may be required for newly imported plant propagating material.

- Some countries, in particular Australia and New Zealand, implement quarantine and assessment requirements for organisms which are newly introduced into the respective countries.

A recently published legal opinion analysed whether existing EU legislation e.g. for seeds, food and feed, pesticides and nature conservation, would provide a suitable framework for the assessment of nGM applications outside the biotechnology legislation for risks to human and animal health and to the environment: SPRANGER (2017) concluded that such sectoral legislation will not provide a suitable framework for an assessment of nGM applications. A premarket assessment of products is either not generally required (e.g. according to the food law) or the required assessments are unsuitable for replacing the comprehensive risk assessment required by the EU biosafety framework (e.g. for novel food laws, pesticide regulations). This conclusion is supported by the results of a study conducted by VOIGT&KLIMA (2017).

Furthermore some general requirements according to regulations for quarantine, phytosanitary measures and invasive alien species only apply to organisms or species, which are newly introduced into a country.

The information gathered from regulatory experts from non-EU countries indicates that the general conclusion drawn by SPRANGER (2017) for the EU also applies to all other regulatory systems: The general requirements applicable to the agricultural use of plants in the different countries do not ensure a risk assessment comparable to that according to the respective national biosafety frameworks. This outcome is independent of the type of regulatory trigger implemented in a respective framework and can also affect systems with particular product-oriented triggers like the USA (KUZMA 2016b, ZETTERBERG&EDVARDSSON BJÖRNBERG 2017).

4.3 Risk assessment requirements for GMOs and nGM applications

This chapter addresses two questions in particular:

3. Is an evaluation of possible adverse effects (risks) required to determine the regulatory status of a specific nGM application in the countries covered in this study?
4. Which standards are implemented for risk assessment implemented for GMOs and nGM applications in the countries covered in this study?

The second question is also addressing whether potential adverse effects associated with nGM applications are addressed during the risk assessment according the respective biosafety frameworks.

4.3.1 **Risk-related considerations for determination of the regulatory status**

Regarding the first question the situation is slightly different between countries which implement process-oriented regulatory triggers and the two regulatory frameworks implementing different product-oriented triggers (USA, Canada).

Under regulatory frameworks with process-oriented regulatory triggers no specific risk evaluation is conducted to determine the regulatory status of applications. Typically decisions on the regulatory status are based on a legal interpretation of the definitions of regulated products included in the respective legislation (see chapter 4.2.1). Most of the analysed

process-oriented triggers outline in a general way the techniques for genetic modification which are covered by the regulation. Some frameworks, including the EU legislation, are providing examples or closed lists of techniques which result in regulated as well as non-regulated products. Furthermore many process-oriented regulatory systems, again including the EU, contain exemptions for products developed with specific methods. E.g. in the EU framework products of mutagenesis and cell fusion are exempted if certain conditions are met (i.e. no involvement of recombinant nucleic acid molecules or GMOs other than those exempted).

According to the details included in the definitions of regulated products the evaluation of regulated status needs to refer to specific technical information concerning the characteristics of biotechnological methods used to generate nGM organisms and the origin of the genetic modifications introduced into these organisms. This information is usually not used for a pre-evaluation of the risks associated with a particular genetic modification. However the implemented definitions themselves may be regarded as an implicit estimation of the potential of the regulated technologies and their products to be associated with risks in relation to the protection goals addressed by the specific regulations.

In process-oriented regulatory frameworks typically techniques which are used in conventional breeding for introducing undirected genetic changes, like random mutagenesis by ionising radiation or chemical mutagens, are exempt from regulation based on the history of safe use of such products or the assumption that the application of such methods is considered to be of negligible risk. In the discussions in Australia on the technical amendments proposed by OGTR the comparability of the modifications induced by specific nGMs (e.g. SDN-1 or ODM approaches for genome editing) with genetic changes induced by exempted technologies is used as an argument that these nGM applications pose similar negligible risks as non-regulated products (OGTR 2016).

In the EU legislation Recital 17 of Directive 2001/18/EC indicates that its provisions should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record. The ECJ ruling confirmed that nGM products that are determined to be GMOs according to Directive 2001/18/EC may only be excluded from biosafety requirements if they meet two conditions specified in the Directive in Annex 1 B and Recital 17; i.e. if the techniques to produce them do not involve the use of recombinant nucleic acid molecules AND if they are obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record. The ECJ ruling confirms that methods of directed mutagenesis (in the particular case via SDN-1) did not meet both conditions and thus do not qualify for exemption (ECJ 2018). The ECJ decision requires that in line with a precautionary approach a risk assessment prior to use needs to be conducted for newly established genome edited organisms. The wide range of genetic modifications which may be introduced by nGMs like genome editing, the limitations of existing knowledge concerning the potential effects of the modified organisms and the difficulties to address the complex interactions of the modified organisms with the environment were reasons for the decision.

According to the US system biotechnological applications are evaluated for plant-pest characteristics and/or whether they are regarded as noxious weeds (RA by USDA-APHIS), or if they exhibit pesticidal properties or environmental toxicity (RA by US-EPA), or whether

they are substantially different in composition or regarding its allergenic, toxicological or nutritive properties (RA by FDA). Upon voluntary request the food safety of biotech applications is confirmed by FDA. nGM applications may also presented to FDA for review (WALTZ 2018). The mentioned triggers indicate which particular risks are considered significant enough to warrant regulation and a requirement for risk assessment of the indicated biotechnological products.

In Canada the developer of a product needs to consider whether an introduced trait is "novel", i.e. not already present in agronomically-used varieties of the plant and whether it might have a potential to result in adverse environmental effects. The CFIA can provide advice in pre-submission consultations and decides on a case-by-case basis on the regulatory status (see chapter 3.5.1). Since the general plausibility of adverse effects is sufficient for the regulator to decide, no detailed pre-evaluation of possible environmental risks is conducted. However the "novelty trigger" can be regarded to cover in a general way applications without a history of safe use. It thus indicates in a general way a relevant level of uncertainty that the regulated applications might be associated with unwanted effects.

4.3.2 Risk assessment approaches for GM and nGM products subject to existing biosafety regulations

An overview on some of the aspects relating to the second question mentioned above is provided in Table 5 below.

As of 2018 no new requirements developed specifically for the risk assessment of nGM applications were implemented in any of the countries covered in the study at hands. Therefore all of the investigated regulatory frameworks currently implement similar approaches for the assessment of health and environmental effects from both GMOs and nGM applications. The general approach to risk assessment does not differ between regulatory frameworks which are based on process- or product-oriented triggers for the determination of the regulatory status of individual products.

These risk assessment approaches are mainly focused on relevant characteristics of the products in question. However considerations based on the methods used to generate products however are used in all assessment approaches as a means to focus the assessment on relevant aspects. Such information is used during problem formulation to determine which risk hypotheses need to be addressed in the risk assessment. This risk assessment is typically conducted in a comparative way, i.e. comparing a modified organism (GMO or nGM plant) against an unmodified counterpart.

The general RA approach used in the EU is also followed by non-EU countries in Europe (Switzerland and Norway) as well as South Africa. It is also broadly similar to the approach outlined in the CPB. The EU approach is based on several requirements: Applicants need to submit a basic data set for molecular characterisation, characterisation of expression of the modified trait as well as the compositional and agronomical characterisation. In addition seven areas of risk need to be addressed by a problem formulation and risk characterisation approach[63]. Identified risks and unintended effects are furthermore addressed by mandatory

[63] (1) persistence and invasiveness of the GM plant, or its compatible relatives, including plant-to-plant gene transfer; (2) plant-to-micro-organism gene transfer; (3) interaction of the GM plant with target

post-marketing environmental monitoring consisting of case-specific monitoring and general surveillance (EFSA 2010).

Also the general approach to RA implemented by Argentina, Brazil, Australia and New Zealand, respectively, is quite similar. However differences exist regarding the requirements for post-authorisation environmental monitoring of unconfined releases (see Table 5).

Table 5: Overview of plants with herbicide-resistance traits developed by nGMs

(CSM: Case-specific monitoring, GS: General Surveillance)

Country	Similar RA for GMOs and nGM appl.	Specific RA standards for nGM applications	Environmental monitoring for GMOs and nGM appl.
European Union	Yes	No	Yes (CSM & GS)
Norway	Yes	No	Yes (CSM & GS)
Switzerland	Yes	No	Yes (CSM & GS)
USA	Yes	No, amendment under discussion	No
Canada	Yes	No, amendment under discussion	No (only for confined releases)
Argentina	Yes	No	?
Brazil	Yes	No	Yes
Australia	Yes	No	Yes (CSM to address identified risks)
New Zealand	Yes	No	Only for conditional approvals
South Africa	Yes	No	Yes (CSM & GS)

Canada is focusing the risk assessment of applications for environmental release on five main areas, including direct and indirect impacts on biodiversity[64]. Information on the identity and the origin of the PNT needs to be submitted for molecular characterization. The risk assessment conducted by the USDA in the USA is based on a case-specific-approach and a problem formulation which takes into account the biology of the modified plant species and the characteristics of the newly developed traits (MCHUGHEN 2016). The scope of the risk assessment is considered to be narrower and less comprehensive compared with the respective requirements in the EU, e.g. regarding consideration of indirect and delayed effects (ZETTERBERG&EDVARDSSON BJÖRNBERG 2017).

organisms; (4) interaction of the GM plant with non-target organisms; (5) impact of the specific cultivation, management and harvesting techniques; including consideration of the production systems and the receiving environment(s); (6) effects on biogeochemical processes; (7) effects on human and animal health.

[64] (1) potential of the PnGM to become a weed of agriculture or be invasive of natural habitats; (2) potential for gene flow to sexually compatible plants whose hybrid offspring may be-come more weedy or more invasive; (3) potential for the PnGM to become a plant pest; (4) potential impact of the PnGM or its gene products on non-target species, including humans; (5) potential impact on biodiversity.

Differences between the analysed systems are rather seen in the extent of information required to address specific risk issues and additional information requirements which may be determined on a case-by-case basis taking into account the specific characteristics of a particular application. Based on the level of experience with a product (or similar products) and on the level of existing information on such products, lesser information requirements may be decided on a case-by-case basis in all regulation frameworks. The USA and Canada are considering amendments, which would introduce a more formalised system for differing data requirements for different applications in the future.

In the EU EFSA has published opinions addressing risk assessment requirements for certain nGMs, like cisgenesis/intragenesis, and SDN-3 genome editing applications (EFSA-PANEL ON GMOS 2012a, EFSA-PANEL ON GMOS 2012b). Also initial work concerning the risk assessment of RNAi applications was published (CASACUBERTA et al. 2015, RAMON et al. 2014). Subsequently to the ECJ ruling the European Commission has mandated EFSA to address RA requirements of other types of nGM applications, namely SDN-1, SDN-2 and ODM applications.

More differences exist between the different regulatory frameworks regarding requirements for environmental monitoring after authorisation. The EU and countries like Norway, Switzerland, Brazil and South Africa require both case-specific monitoring (CSM) to monitor identified risks as well as general surveillance (GS) to detect unanticipated environmental effects, using different measures of implementation. The current system for post market environmental monitoring in the EU is criticised for several reasons: CSM is rarely used to address uncertainties encountered during the risk assessment or to monitor the exposure of the environment; GS is too unspecific to address particular environmental parameters and is not making appropriate use of existing systems for environmental monitoring (e.g. Züghart et al. 2011).

Other legislations like USA and Canada do not require post-marketing monitoring for unconfined releases. Australia is only implementing CSM and New Zealand is requiring monitoring only for a specific type of authorisation, i.e. conditional use permits. However it is currently unclear whether the monitoring measures implemented for conditional releases will generate appropriate and meaningful results (SCNZ pers. comm.).

Again GMOs and nGM plants which are subject to the respective biosafety regulations are or would be treated similarly regarding the above mentioned issues.

5 Analysis and discussion

The comparison of the different legal frameworks for the regulation of biotechnology applications indicates that the emerging use of nGMs in plant breeding poses a number of legal and technical challenges.

Due to the fast pace of technological development the spectrum of available nGMs is expanding rapidly; this e.g. might extend the range of possible traits to be developed, increases the specificity of some techniques and the speed of development, and makes some techniques like approaches for genome editing cheaper and more easily accessible to developers. However this means that the regulating bodies are and will be confronted with a growing spectrum of nGMs and nGM applications with different characteristics for their consideration.

Most of the existing regulatory frameworks for biotechnology applications were developed to regulate products generated by classical GM-technology in the 1980ies and 1990ies. Administrative systems based on these regulations were implemented in the different countries and revised based on the practical experience with their application. All the different systems implemented by the different countries are generally considered to be fit for the purpose of regulating GMOs, despite an acknowledged need for further refinement and regular review. However there are concerns that ambiguous definitions of regulated products and an inconsistent scope of regulation, particularly concerning nGM applications, may jeopardise the existing process-oriented regulatory approaches, like the EU regulatory system (JONES 2015b, ZETTERBERG&EDVARDSSON BJÖRNBERG 2017).

An important question is whether the existing systems are also appropriate to address the range of nGM applications and provide appropriate and workable procedures for regulation and risk assessment. According to the Swiss ECNH (2016) this risk assessments should be commensurate with the level of risk posed by different nGM applications and take into account the available knowledge on and the scientific uncertainties associated with these nGM applications (ECNH 2016).

A crucial aspect is also whether the regulatory triggers which were devised and implemented a considerate time ago are also appropriate for the existing and newly emerging nGM applications. Therefore it has to be questioned whether the existing regulatory triggers need to be adapted in response to the recent technical developments.

For those reasons all of the studied countries intensely discuss whether and how their regulatory systems need to be further developed to address the challenges presented by the application of nGMs for plant and animal breeding. The respective discussions started quite early in most countries, e.g. a dedicated EU-level working group was established in 2007 to address the issue, and activities for information exchange between countries at the OECD level were established back in 2013. However the discussions are still ongoing and intensifying as many relevant issues are not yet resolved in most countries. This is indicated by a growing body of publications addressing the respective regulatory challenges and the vast number of high-level events devoted to these discussions, e.g. the 2018 OECD conference on the topic (FRIEDRICHS et al. 2019).

The challenges are manifold due to the diverse range of relevant nGMs and the increasing number of different applications developed with these techniques (VOGEL 2016, SAM 2017).

These techniques are able to induce

- different types of genetic modifications, which are more or less comparable to transgenic modifications present in regulated GMOs,
- modifications in different plant species, with different biological characteristics, and therefore a different potential for environmental and health effects,
- modifications in intermediate as well as final breeding products,
- stably heritable or transiently present modifications and
- modifications of whole plants or only of certain plant parts.

Additionally a wide range of traits may be developed in different plants, including among others herbicide-resistant crops, disease- or pest-resistant plants, plants with modified composition, plants with modified reproductive behaviour or morphology and plants with enhanced tolerance against environmental stress, e.g. draught, salinity, etc (MARTÍNEZ-FORTÚN et al. 2017, MODRZEJEWSKI et al. 2019, SEDEEK et al. 2019). Again it must be taken into consideration that the traits developed by nGMs can be associated with a variable potential to result in unintended effects (ECKERSTORFER et al. 2019b).

The results of this study underlines that the regulatory interest is presently focused on applications developed by different genome editing methods, in particular CRISPR-based methods for genome editing (as well as genome editing by other site-directed nuclease systems like TALEN and ZFN; and ODM methods). In addition other nGMs are considered regarding regulatory issues, in particular risk assessment, among them cisgenic- or intragenic organisms, RNAi-applications, applications involving GM-breeding intermediates but result in non-transgenic breeding products (e.g. accelerated breeding/flowering induction, sterility induction for production of hybrid seeds, SDN-genome editing applications with intermediates containing transgenic SDN-expression cassettes). Other nGMs, including RdDM, transgrafting and reverse breeding, are of lesser interest.

5.1 Process vs. Product

The regulatory challenges posed by these nGMs are different for regulatory frameworks which implement fully or partly process-oriented regulatory triggers (EU, Norway, Switzerland, Argentina, Brazil, Australia, New Zealand, South Africa) or those implementing partly or fully product-oriented regulatory triggers (USA, Canada).

For the sake of conceptual clarity the terms process- and product-oriented are used only in relation to the nature of the regulatory trigger employed by a specific regulatory framework in this study.

In the literature these terms are sometimes used differently, e.g. in relation to the entities regulated by biosafety legislation (MCHUGHEN 2016, RICROCH et al. 2016, SCHUTTELAAR 2015). However in all investigated legislation the regulated articles are the “products” of the biotechnological modification process, i.e. the biotechnologically modified organisms or any products derived from these organisms.

In other contexts the terms are also used in relation to the approaches used for risk-assessment in different regulatory frameworks, i.e. whether the risk assessment is focused

on the characteristics of the biotechnologically modified organisms or products or on the effects resulting from the used technologies (MCHUGHEN 2016). As discussed by KUZMA (2016) such a dichotomy is however not considered to be helpful from a scientific standpoint. KUZMA (2016) argues that these issues are not distinct in relation to risk assessment, since the traits of products depend in part on the characteristics of the methods used in their development. This study demonstrates that all of the covered regulatory frameworks acknowledge this in their approach to risk assessment. Thus most of the analysed regulatory frameworks include formal requirements for submission of information on the methods, which were used to establish these organisms. Such information usually needs to be submitted together with the molecular characterisation of the modified organism which is notified for authorisation. This information is used by notifiers and regulatory bodies for problem formulation to address all relevant risk issues, including an assessment of possible unintended effects. Even regulatory frameworks which are based on product-oriented regulatory triggers, like the Canadian system, ask for and use such information for risk-assessment of PNTs. In addition Canada also worked on projects directed to elucidate and characterise method-related unintended effects (LADICS et al. 2015) with a view to respective risk assessment requirements.

However, even when the terms process- and product-oriented are strictly used in relation to the denominated regulatory triggers, the classification may be challenging to apply. This is particularly seen with definitions, which were devised in the 1990ies to differentiate GMOs from plants developed with conventional breeding methods, including classical forms of mutagenesis. E.g. the wording of the definition contained in the EU regulations, particularly in Article 2 of Directive 2001/18/EC, is interpreted differently either as unequivocally process-oriented (SPRANGER 2015, KRÄMER 2015) or as both process- and product-oriented (KAHRMANN et al. 2017). Similar difficulties were encountered in other countries which based their regulatory frameworks on comparable definitions and include specific exemptions, e.g. for products developed by (undirected) mutagenesis.

As the definitions included in some regulations are not entirely self-explanatory regarding nGMs like genome editing, they need to be interpreted by the respective competent authorities. These interpretations are not always accepted by all stakeholders, as demonstrated by discussions addressing the court decisions in New Zealand and particularly at the ECJ (PURNHAGEN et al. 2018, URNOV et al. 2018, WASMER 2019).

5.1.1 **Challenges for regulatory frameworks implementing process-oriented triggers**

In contrast to the situation encountered with classical GMOs the used process-oriented trigger definitions are not specific enough to enable straightforward and unequivocal decisions concerning the regulatory status of the above mentioned nGM applications. For the EU regulatory framework the different opinions included in the report of the EU-level working group on new techniques (NTWG 2012) concerning the regulatory status of most of the analysed examples for nGM applications demonstrate the challenges. The recent dispute on the regulatory status of genome edited herbicide-resistant oilseed rape established by ODM is another example (BVL 2015, KAHRMANN et al. 2017, KRÄMER 2015, SPRANGER 2015).

However the easy differentiation between regulated and non-regulated products is regarded as an advantage of regulatory systems based on process-oriented trigger definitions as

compared to other regulatory frameworks, which implement product-oriented triggers. Such product-oriented regulatory systems typically require an evaluation of each application to determine its regulatory status.

For most of the regulatory frameworks which implement fully or partial process-oriented regulatory triggers no broadly accepted policies are yet available and implemented concerning the applicability of the respective regulations for most nGMs (see Table 4). In the meantime the competent authorities have to evaluate specific nGMs and applications developed by these nGMs individually to determine their regulatory status. Thus the mentioned advantage is lost and the decisions also may not be considered more predictable than decisions based on a product-related trigger. In this respect two relevant issues stand out:

- First, it is important which authority is in charge of deciding on the regulatory status. Typically such decisions are taken by the same authorities that decide on the authorisation of such products. However authorities may not have the legal mandate to issue decisions based on their interpretation of the respective definitions and thus make decisions which redefine the scope of regulated articles. E.g. in New Zealand some stakeholders disputed the mandate of the competent authority to make wide ranging interpretations of the existing law to reach decisions. A court ruling supported these concerns and determined that decisions which change the scope of the law should only be due to a national decision on policy. If courts are involved to review administrative decisions they need to consider a high number of complicated legal and technical arguments, which may result in substantial delays in decision making.
- Second, only limited guidance for decision-making is usually available to the authorities tasked with the interpretation. Most of the analysed regulations are not specific enough to provide sufficient guidance for all nGM applications that need to be considered in that respect. In absence of appropriate legal criteria the New Zealand government chose to regulate all contentious nGM applications until a future policy has been decided in parliament. This in effect is amounting to a broad interpretation of the regulatory trigger with exemptions only being granted for exactly defined cases (e.g. mutagenesis induced by radiation or chemical mutagens). South Africa is pursuing a similar approach and is applying its definition in a broad interpretation until the national policy on nGM applications is further determined.

However, if decisions were taken on the inclusion or exclusion of certain techniques in a process-oriented framework, the trigger becomes easily applicable and transparent.

5.1.2 **Challenges for regulation frameworks implementing product-oriented triggers**

An overall advantage of systems using product-oriented triggers in principle is that the respective competent authorities are responsible for regulation of all products with similar characteristics, irrespective of the methods which are used for their development. This is supporting the consistent implementation of the legislative requirements to ensure similar oversight for comparable products. E.g. plants with new traits for resistance to herbicides developed by either conventional breeding, nGMs or GM technology are regulated similarly as PNTs in Canada, whereas in frameworks with process-oriented regulatory triggers the regulatory oversight may be different for such HR plants containing similar traits, but

developed by different techniques. Therefore nGM applications – existing as well as emerging ones – readily fit into the context of the existing PNT regulations in Canada and are not considered to present a serious challenge for the regulatory framework (WOLT 2017).

Novelty determination in Canada turned out to be challenging in specific cases. Not all traits can be easily determined to be either strictly "novel" or conventional. E.g. among others the question arises whether plants which are developed independently to contain traits which are broadly comparable, but not exactly similar need to be considered novel. Furthermore "novelty" is not used as the only characteristic, but the trigger also refers to the possibility for risk associated with a novel product. Thus the authorities have to choose a threshold on the "riskiness" continuum in their regulatory decisions (MCHUGHEN 2016). Currently the general plausibility for risk is used by the CFIA to decide that regulation is required, however the regulations contain no specific criteria to support decision making for both trigger components. The apparent lack of appropriate criteria and guidance is therefore also a relevant issue for product-oriented regulatory systems.

The existing US legislation applied by USDA-APHIS intends to focus on product-related risks, however, in practice it does not achieve full consistency in this respect. KUZMA (2016) notes, that for the majority of regulated products it is the process of the employed GM technology that has triggered regulatory requirements. Also other recent reports note that due to the specifics of the employed trigger the current APHIS system is involving a de facto process-based trigger, while being considered to be product focused (WOLT 2017). It is described as "a strange patchwork of rules and exceptions" and can be considered a hybrid of process-oriented or "method-based" according to the terminology used by STRAUSS&SAX (2016) and product-oriented reasoning (MCHUGHEN 2016, STRAUSS&SAX 2016).

Another concern is that the scope of regulated products lacks consistency, e.g. for GM plants products which similar traits, but which are developed by GM technology with or without *Agrobacterium*-mediated transformation methods or genetic components derived from plant viruses (MCHUGHEN 2016, NAS 2016). It is also noted that in recent years a growing number of products was determined as not regulated due to the use of different transformation methodologies not involving *Agrobacterium*-based tools by the developers (KUZMA 2016a). Some of these non-regulated plants contain similar traits as plants which were previously regulated (e.g. transgenes which induce resistance against commonly used herbicides like glyphosate).

5.1.3 General advantages and disadvantages of product- or process-oriented regulatory triggers

An issue of discussion is whether regulatory systems based on either product- or process-oriented regulatory triggers may be more advantageous for the regulation of nGM applications (SPRINK et al. 2016b)? We analysed the available information and interviewed regulatory experts concerning their views. A non-exhaustive overview on the perceived general advantages and disadvantages of both systems is presented in Table 5. Some pros and cons are not specific for nGMs, but also relevant for the regulation of GMOs according to the existing systems.

The analysis shows that both trigger systems have a number of generic advantages and disadvantages. Experience in the analysed countries demonstrates how important the

specific details of implementation of the basic concepts are for the workability of both regulatory approaches. Thus as also noted by KUZMA (2016b) neither system can be regarded as superior at a general level.

Table 6: General analysis of the pros and cons associated with regulatory systems for biotechnology applications implementing product-oriented and process-oriented regulatory triggers

If advantages/disadvantages are relevant for a specific group of products (nGM products or GMOs) this is indicated in parenthesis in the particular fields.

Product-oriented triggers		
Perceived advantages	**Perceived disadvantages**	**Challenges (Examples)**
High flexibility to accommodate products of emerging technologies without need for legislation change (nGMs)	Some product-oriented triggers may result in inconsistent coverage of products with comparable traits (USA: nGMs and GMOs)	Different competent authorities may be involved, if a broad scope of use is intended (env. release and food/feed use), shared responsibilities, need for coordination
Existing regulatory structures can be used for comparable products	Individual applications may need to be reviewed for regulatory status	Criteria and guidance required for decision making on regulatory status
Similar regulatory approach for comparable products developed by different techniques	Process to determine regulatory status considered more complicated and less predictable compared with process-related triggers (GMOs)	Limited compatibility with regulatory systems based on process-oriented triggers regarding the scope of regulated articles
Consistent risk assessment perspective for products irrespective of the method of production	The typical remit of existing authorities may be ill-suited to address risk assessment challenges of emerging applications	
Process-oriented trigger		
Perceived advantages	**Perceived disadvantages**	**Challenges (Examples)**
Typically new sectoral legislation is introducedand implemented by a specific authority	Limited flexibility to accommodate products of emerging technologies – possible need for legislation change in reaction to technological developments (nGMs)	Severe challenges of trigger interpretation regarding some NTs if specific guidance is not available
Newly introduced sectoral regulations address all relevant risk assessment requirements	Regulation gaps until newly emerging technologies are addressed by trigger amendments (nGMs)	Ambiguous trigger definitions may lead to interpretation conflicts that have to be settled by administrative and/or court proceedings (nGMs in particular)
Process-oriented triggers considered easier to implement and more predictable (GMOs)	Trigger specifics (exemptions) may result in inconsistent coverage of products with comparable risk (nGMs)	Limited compatibility with regulatory systems based on product-oriented triggers regarding the scope of regulated articles

However systems based on product-oriented triggers are considered more flexible when it comes to products developed with newly emerging technologies, without the need to repeatedly adapt existing legislation. Frameworks based on product-oriented triggers may strengthen consistency in the regulation of products with comparable characteristics. This

however depends on whether a particular system indeed achieves consistent coverage of products associated with comparable possible risks. The US regulatory framework shows that specific product-oriented trigger definitions can result in an inconsistent range of regulated products: e.g. *Agrobacterium*-mediated transformation results in regulation by USDA, while transformation with similar transgenic constructs of non-plant pathogenic origin by particle bombardment does not (NAS 2016). The current distribution of responsibilities in the USA between existing authorities also results in emerging biotech products being regulated by authorities that have an inadequate regulatory focus for such products, resulting in particular challenges in addressing issues of greatest concern during risk assessment (KUZMA 2016a). Product-oriented triggers require a separate determination of the regulatory status for each specific application, which is considered by the interviewed regulatory experts to be more laborious and complex for involved authorities.

A main advantage of frameworks based on process-oriented regulatory triggers is that they provide a clear and straightforward means to establish the regulatory status of classic GMOs both for developers and authorities. The establishment of specific authorities with a consolidated responsibility for all matters of sectoral biosafety legislation can provide a better framework to prevent regulatory gaps and to ensure that a comprehensive risk assessment approach is implemented. These systems however are significantly challenged by several types of nGM applications, particularly products developed by genome editing, if existing definitions are ambiguous. Without concrete policy and appropriate criteria for interpretation, lengthy legal disputes e.g. as in New Zealand and the EU can occur, delaying decisions on individual applications as well as policy development.

An adaptation of process-oriented triggers to ongoing technical developments typically requires the repeated introduction of specific amendments in response to technological developments. Such amendments may need considerable time for their introduction, e.g. for consultation and implementation, and this might cause a temporal regulatory gap for the respective nGM applications. Trigger definitions covering a very broad scope of applications might potentially be flexible enough to avoid the development of regulation gaps, however at the expense of a higher number of applications which need to be assessed for risks by the competent authorities.

Our analysis indicates that the specific details of a particular trigger are more important than the general choice of either a product-oriented or a process-oriented system. The respective differences of implementation result in:

- significantly different ranges of regulated products, particularly of nGM products,
- different levels of regulatory uncertainty to determine the status of regulation of specific (nGM) products,
- different levels of consistency to address comparable risks of products developed by different technologies (including GM technology, nGMs and conventional breeding).

Further discussions should therefore not only focus on the question whether a system is based on a process- or product-oriented trigger. The implications of the specific details of existing or proposed trigger definitions on the range of regulated articles also should be taken into account when judging the advantages or disadvantages of a particular system.

It is noted that only some product-oriented systems, like the Canadian Plant with Novel Traits-regulations, implement a similar regulatory approach for all novel products irrespective of the methods used for their development and consistently regulate novel biotech crops as wells as novel plants produced by conventional breeding methods.

5.2 Transparency of decision-making

Transparency of decision-making is an important issue for all regulatory approaches implementing process- as well as product-oriented regulatory triggers. This is acknowledged by regulators from all of the investigated countries. However most of the legislations do not provide the means for ensuring transparency. Only in the USA all regulatory decisions taken on submissions for the determination of regulated status to USDA-APHIS are publicly available irrespective of whether the respective applications are found to be subject to regulation or exempted from regulation [65]. In other countries like Canada as well as countries with process-triggered regulation transparency is provided only for the applications which are determined to be regulated.

However, informing the public about the regulatory status of biotech applications and in particular of nGM applications is regarded as a matter of crucial importance. Even experts calling for decreasing the level of regulatory oversight of biotechnology applications in the USA support that a registry of all applications should be established and maintained (STRAUSS&SAX 2016). Such a registry should also include applications which have differing regulatory status in varies countries (e.g. SDN-1 in Argentina, Brazil and the USA compared to the EU and New Zealand). With a view to international trade and the varying regulatory status of comparable nGM applications, access to this information will be highly important.

The regulatory status of nGM applications is in the process of being resolved in a growing number of countries by administrative or judicial decisions based on the existing biosafety laws and by introducing supplementary regulations specifying concrete criteria for such decisions. However, the lack of harmonisation at the global level concerning such approaches will lead to situations that identical biotechnological applications/products are assigned opposing different regulatory status in different jurisdictions, and thus aggravate the lack of harmonisation that is already present in the GMO sector. This will result in a serious challenge for international trade between such countries. To address this challenge transparency in decision-making for nGM applications is a crucial issue acknowledged by regulatory experts from all investigated frameworks. We consider a public international registry which includes all biotech products that are placed on the market, among them (nGM) applications exempted in certain countries from regulatory oversight and risk assessment prior to commercial use, to be essential. This would ensure that all countries are enabled to identify products developed by nGMs, if their respective legislation requires them to do so. Non-registered and undescribed products developed by certain nGMs, e.g. SDN-1 type genome editing, can be difficult to detect and keep track of. Shipment of agricultural products suspected to be of uncertain composition, i.e. containing nGM products, could provoke unwanted disruptions of international trade.

[65] Only products with unclear status are submitted to the „Am I regulated“ process

We note that the Biosafety Clearing House (BCH) according to the CPB is an existing registry for GMO applications at the international level that also contains information voluntarily submitted by non-parties to the Protocol. It may also provide an appropriate framework for the purpose of sharing relevant information on nGM applications. We are, however, aware of the fact that it will be a challenge to establish and maintain a registry including nGM applications, which are not subject to regulation according to some national biosafety frameworks, since active voluntary cooperation of country administrations and developers is required. Nevertheless stakeholders from all countries should be aware that sharing information on nGM products will be vital, since global harmonisation of regulatory approaches towards applications of genome editing and other nGMs will not be easily achieved in the near future.

5.3 Options for regulating nGM applications

The challenges posed by nGM applications regarding the determination of their status of regulation may be addressed by a range of possible options. The following options are considered by the countries covered in this study, however the analysis indicates that only few of the above options are applied or may be applied by most of the investigated countries. In that respect it is important to note that only in a few countries applications for different types of nGM applications were submitted for regulatory decisions yet; in most of the countries many nGM applications are currently only used for research purposes in contained use or in field trials and no submissions for unconfined commercial use were made.

In summary our analysis indicates that the following approaches are used or may be used when countries wish to provide regulatory oversight for nGM applications:

1. Existing regulatory framework for GMOs is applied to nGM applications
    a) For all nGMs (South Africa) or for certain types of nGMs (EU)
    b) Based on case-by-case decisions on individual nGM applications (USA, Canada)
2. Technical revision of existing regulations (definitions and exemptions) (New Zealand, Australia)
3. Implementation of supplementary legislation supporting the existing framework to clarify aspects related to regulation of nGM applications (Argentina, Brazil)
4. New stand-alone legislation for nGM applications, in addition to existing legislation for GMOs (option, no example available)
5. “New” overall framework for all biotechnology applications (option, no example available).

So far, a significant number of countries have not introduced specific legal instruments for nGM applications and have been using the existing regulatory framework to deal with such applications. In countries with product-oriented triggers individual applications are evaluated at a technical level to determine whether they are covered by the criteria included in the respective legislation (option 1b). The investigated countries with product-oriented triggers operate in that way by default and will probably continue to do so. At least in Canada there are no intentions to change the existing approach to regulation (CFIA pers. comm.).

Also most of the countries with process-oriented triggers will implement an approach to legally clarify the status of individual nGM applications (option 1a). In these frameworks such an approach will provide decisions which may be of predictive value for the regulation of other applications using similar technologies. However some crucial challenges need to be addressed in this respect. First of all and given the various challenges outlined in this study this approach will not be easy to implement for the respective competent authorities and cannot be assumed that the results will be accepted by all stakeholders. As demonstrated in New Zealand and the EU such decisions may indeed only be settled at supreme courts.

In addition decision making based on clarifying the regulatory status of groups of applications developed by certain nGMs will not allow to specifically single out applications associated with risks and subject them to risk assessment prior to use. Due to the focus on technology-related considerations such groups of applications, e.g. applications of SDN-1 genome editing, will comprise applications associated with different degrees of risk due to the characteristics of the different traits developed with a particular nGM.

Only countries which choose to regulate all nGM applications will probably consistently regulate all risk-relevant applications. However if a high number of applications including ones associated with a lower degree of risk is subject to regulation such an approach may turn out to be impractical for resource reasons (KUZMA 2016b).

Option 2 was used by Australia to address the regulatory status of different types of genome editing applications and is also considered by other countries. The technical amendment of specific elements of the respective regulatory trigger may address some challenges with some nGMs of specific relevance. However due to the time and efforts needed for proposal development, consultation and implementation the approach will lag behind technical developments. The approach is also not very flexible regarding emerging new method variants and developments. Newly developed method variants may then necessitate another round of amendment. E.g. how to address serial or multiplexed applications of nGMs, like genome editing, is not discussed in the current technical review of the trigger definition in the Australian GTA, but will be further discussed during the broader review of the GTA (OGTR pers. comm.).

The Australian revision of the scope of the current regulation also shows that such amendments may not help to achieve consistent regulation of applications of comparable risk. The proposed exemption of SDN-1 applications for genome editing while regulating ODM and SDN-2 applications may be best in line with the current legal approach and its implementation. However it cannot be considered fully consistent from a risk-based perspective, since SDN-1 and SDN-2 or ODM-applications, which can generate products with comparable genetic modifications, might nevertheless be treated differently.

If only the trigger definitions or exemptions are amended and no risk-related differentiations are included, the regulated nGM applications will be subject to the same risk assessment as GMOs and non-regulated applications like in Option 1 will only be subject to general requirements which may not particularly suited to address specific risk-issues.

Option 3 as used by Argentina, Brazil and other South American countries (LEMA 2019) offers an increased possibility for introducing more general adaptations and thus to address a wider range of nGMs. This option may be used for the introduction of specific regulatory procedures for decision-making on the regulatory status of nGM applications. Depending on

the general legislative framework of a given country this option might involve more procedural effort to be implemented compared with the introduction of technical amendments into existing legislation. Otherwise similar challenges as noted above for Option 2 apply.

The last two possible options (Introduction of new stand-alone regulations for nGMs in addition to the existing GMO legislation or introduction of a new overall framework for all biotechnology applications including nGM-applications) were not used by any of the investigated countries.

Option 4 would provide the opportunity to introduce legislation for nGM applications, which can be different from existing GMO legislation, e.g. in terms of the regulatory trigger or in terms of regulatory requirements for assessment and management. However, implementing this option would mean that another road of regulation is created in addition to the existing GMO regulations.

Option 5 would lead to the introduction of a newly established regulatory framework to address a wider range of biotechnology products within a harmonised framework which also may feature a different regulatory trigger than the existing GMO legislation. However this has not happened in any country with an established biosafety framework with a longer history of implementation.

Options 4 and 5 would amount to a substantial change of the existing regulatory landscape. They would also probably impact or disrupt the existing operational structures implemented under the current regulatory systems.

The introduction of regulation frameworks implementing product-oriented triggers in the USA and Canada cannot be considered to constitute examples for such a change, since both countries didn´t have specific legislation to regulate biotechnology applications like GMOs before. However introduction of regulations based on a product-oriented trigger for nGM-applications or for all biotechnology applications (including GMOs as well as nGM-applications) in the EU, like outlined as a future possibility by (ZETTERBERG&EDVARDSSON BJÖRNBERG 2017), would constitute a significant system change, requiring manifold changes to procedures and responsibilities which are in place for a substantial time-period.

In the absence of legislation-based governance for nGM applications like genome editing, the implementation of procedures for assessment or use of nGM applications by a cooperative governance network of stakeholders for such technologies was proposed as a possible first step to overcome regulatory uncertainties (JORDAN et al. 2017). While such an approach is not considered to provide a fixed or permanent solution, it is viewed as an option to enable a structured debate and a means to more broadly address the issues associated with emerging agricultural technologies, like genome editing-applications (JORDAN et al. 2017).

5.4 Risk-related considerations

Regulated nGM applications should be subject to a comprehensive risk assessment to address the full range of potential adverse effects, including effects due to plant x trait x environment interactions and unintended effects due to the overall procedures used for the development of new plant lines by nGMs (BUJNICKI 2017, SAM 2017). This notion is also underlined by the conclusions of the Swiss ECNH drawn from a risk-ethics perspective

(ECNH 2016). According to the ECNH a similar risk assessment approach as currently implemented for GMOs should be used for nGM applications, i.e. a probabilistic risk assessment against a background of limited knowledge and lacking experience of safe use.

According to other opinions the assessment of nGM applications in a process-oriented approach should only focus on the specific risks due to the methods used for modification (MCHUGHEN 2016). However such a narrow approach is not or would not be used in any of the investigated frameworks for the regulation of nGM applications. According to BUJNICKI (2017) such an approach would also not be considered to be appropriate for the development of a biosafety approach for nGM applications in the EU.

In addition the study underlines that only the biosafety frameworks, which are currently existing in all the investigated countries, would provide for an appropriate risk assessment for nGM plants, which is addressing all relevant risk issues. The general legislation for plants, which are not covered by the biosafety legislation, is not considered to provide suitable tools to ensure a sufficient risk assessment prior to their unconfined release into the environment, e.g. for commercial use in agriculture.

The finding that some nGM applications are difficult to detect with the available analytical methods does not constitute an argument that these plants cannot be risk assessed. The Canadian legislation mandates that a risk assessment for a PNT product is conducted, but does not require that the developers of the PNT submit a detection method. This indicates that risk assessment requirements can still be implemented for nGM applications for which an analytical identification method is not available. Absence of the ability to detect nGM applications therefore does not provide justification to exempt such plants from risk assessment. However an inability to detect such applications might present challenges for regulatory frameworks, which also include requirements for labelling and traceability.

6 Conclusions

The following conclusions indicate a range of aspects which should be considered further in the course of the debate on possible regulatory developments in the EU with a view to the different approaches that may be applied to resolve the current problems.

The study at hands indicates a number of general challenges to devise and implement appropriate approaches for biosafety regulation. A crucial issue is that such a system needs to focus attention and resources, available e.g. for risk assessment, towards applications which may be associated with a higher potential of adverse effects in light of the limited present knowledge available for most of the present or emerging nGM applications.

In addition other general issues are considered which are of importance for all regulatory systems. Examples include the level of transparency regarding the decisions taken by authorities on the regulatory status of individual nGM applications, or challenges created by different regulatory requirements in different legislations for the international exchange of agricultural goods.

6.1 Concrete criteria for decision-making on the regulatory status of nGM applications are needed

Our study indicates that a lack of specific criteria to aid the determination of the regulatory status is detrimental for regulatory systems. For systems based on product-oriented triggers such criteria can support the necessary interpretation by the authorities in their decision-making on individual applications. In case of process-oriented triggers the development of further criteria can support the work of authorities to deal with definitions of scope which are not automatically discriminative regarding certain nGMs in the absence of a general policy addressing the respective issues. Availability of criteria would relieve authorities from having to provide an interpretation of the respective legislative provisions without guidance and thus to determine regulatory policies by their decisions.

A number of countries discuss or have already implemented such criteria to narrow or broaden the scope of regulation. Argentina and Brazil introduced additional criteria with the supplementary regulations for nGM applications; however no sufficient experience from practical application is available for an evaluation whether this approach is workable for the full range of nGMs that need to be addressed. A better specification of details for techniques to be covered or exempted as proposed by Australia will likely introduce some clarifications. However the proposal only addresses a specific spectrum of nGMs and will not settle issues for the other nGMs not addressed in this step.

The decision of the New Zealand government to better specify the exempted techniques for mutagenesis on the other hand clarified the broad applicability of the HSNO act for a whole range of existing nGMs. The ruling of the ECJ determining that products of new mutagenesis techniques (i.e. genome editing applications) are subject to the requirements of Directive 2001/18/EC addressed the uncertainty concerning the regulatory status of these nGM applications.

6.2 Risk-oriented considerations for different regulatory approaches

Both product- as well as process-based regulatory triggers can be considered to be risk-oriented, however in their own specific ways:

Product-oriented triggers either include a general requirement for the regulation of products which might be associated with a range of risks or they refer directly to specific product characteristics, which are associated with particular unwanted risks. However no pre-evaluation of the riskiness of the particular products is conducted according to the current regulatory frameworks in the USA and Canada. According to the US regulatory system the level of risk is inferred from the overall characteristics of the parental organisms, which are either modified or provide the source of genetic material used for modification. In Canada the plausibility of a risk that the protection goals included in the PNT regulations are impacted is sufficient to trigger regulation if the nGM application is also exhibiting novel traits.

Novelty, the second trigger element in the Canadian framework, can be regarded as an indirect indicator for a general lack of experience with such traits and a missing history of safe use for the novel products.

Both novelty- as well as process-oriented triggers relate to risks in an abstract way. This is however sufficient to provide legal grounds for regulation, which cannot be considered arbitrary.

However the choice of product- or process-oriented regulatory triggers in different regulatory frameworks is not the only aspect, which determines how risks of nGM applications will be considered according to the different frameworks. Of significant importance are the following additional aspects:

The scope of regulated products can be defined either more broadly or more narrow in product- as well as process-oriented systems frameworks. E.g. use of a broad definition of encompassed risk issues (e.g. Canada) versus only specific risk issues to define regulated products (e.g. USA) or a novelty definition which comprises all traits that are actually not occurring in natural populations versus only traits, which may not occur under in nature. On the other hand general, far-reaching definitions of covered biotechnological techniques can result in inclusion of all breeding technologies other than those based on natural reproduction (e.g. Brazil, South Africa) versus a more specific definition of regulated technologies (e.g. Australia, EU, etc.). In process-oriented systems the scope of regulated products can be narrowed by exemptions included in the respective legislation, which can exclude a range of nGM applications from the scope (e.g. Argentina).

Furthermore the range of applications covered by a regulatory framework is also influenced by the criteria set in the legislation for the particular trigger system to be invoked. Loosened criteria applied to either a product- or a process-oriented trigger will result in more applications to be regulated, whereas more rigorous criteria will lead to fewer applications being covered. E.g. in the context of product-oriented frameworks consideration based on general plausibility of adverse effects (e.g. Canada) will be more inclusive as systems based on confirmed risks for source organisms (e.g. USA). Likewise a higher level of experience required to grant non-novel status, e.g. based on previous use of similar traits in agricultural crops will be more inclusive compared with exemptions based on possible occurrence of respective traits in nature. In process-oriented systems different thresholds may be achieved

based on whether a certain technology is applied at any point in the development process (e.g. EU) or whether transgenic modifications need to be present in the final breeding product (e.g. Argentina).

Finally the level of requirements regarding risk assessment and/or the extent of other requirements, e.g. for time-limited consent with mandatory reassessment, or the level of risk management measures differs between the different regulatory frameworks. Whereas the general approach used for risk assessment is comparable in the analysed countries, a higher level of requirements for risk assessment, e.g. concerning the amount of information required for assessment and the need to implement specific guidance, can result in a more in-depth assessment of risks. Additional oversight during risk management, e.g. concerning monitoring, may facilitate the early identification of adverse effects under conditions of unconfined use. The available information on a product needs to be thoroughly analysed to achieve a better level of risk characterisation and insufficient implementation of monitoring requirements will not achieve the intended purpose.

The choice of a product-oriented or a process-oriented trigger system in itself is therefore not the only factor to ensure that nGM applications are appropriately assessed in relation to their potential for adverse effects. The study at hands indicates that risk assessment approaches are typically independent from the used type of trigger. However, with a view to risk assessment a crucial issue is whether applications are subject to biosafety regulations or not. In all analysed countries the assessment requirements concerning biosafety differ very much between nGM applications covered by a biosafety framework and for applications, which are exempt from the existing biosafety legislation. The latter products are only covered by general legislation which typically either does not mandate case-specific risk assessment of individual products for biosafety issues, or which only provides a risk assessment with a different focus (e.g. seed quality instead of biosafety) or with a less comprehensive scope (e.g. novel food requirements which do not include assessment of environmental effects). Therefore no alternative framework is in place in the analysed countries which would ensure that the potential environmental hazards of nGM applications are appropriately considered.

6.3 Transparency on nGM applications is a crucial aspect

The degree of transparency regarding the regulatory approach and the decisions taken in a specific framework are a relevant issue. In conclusion the results of this study suggest that a high degree of transparency regarding all of the following aspects should be provided:

1. Full transparency on the aims, the processes and the remit of the competent authorities of the overall framework, which is implemented for regulation.
2. Participation of the public in reviews of existing regulations, e.g. through consultations.
3. Transparency on criteria for decision making regarding the status of regulation of specific products.
4. Transparency concerning the decisions on the regulatory status of specific products and the justifications for designation as regulated or non-regulated products.

5. Transparency regarding the basis for risk assessment, the process followed for risk assessment, the criteria applied for the determination of risks and the results of the assessment process.
6. In case different considerations need to be taken for decision making, e.g. consideration of biosafety as well as socio-economic aspects, transparency needs to be achieved how an overall decision is reflecting the different aspects.

Some of these recommendations are already addressed in various countries to different degrees at present, particularly regarding the first two issues. However sufficient transparency is still lacking regarding the criteria for making decisions on the regulatory status of specific products in most countries. Only some countries have fully developed detailed criteria to guide this process, least have them included in their legislation and tested them in practice. E.g. it needs to be seen whether the criteria included by Argentina in their supplementary regulation on nGM applications will be sufficient for the purpose at hands.

Regarding the fourth issue, transparency in most countries is limited to information on regulated applications. Only APHIS is publishing the results of the process for determination of regulatory status for non-regulated products as well, most other countries do not disclose this information. However transparency on this issue is regarded particularly important (STRAUSS&SAX 2016).

In that respect we argue that further efforts to support international information-exchange on nGM applications are essential. This concerns among others the establishment of a public international registry as outlined in chapter 5.2. Such a registry should include all biotech products that are placed on the respective market(s), among them (nGM) applications exempted in some countries from regulatory oversight and risk assessment prior to their commercial use. Stakeholders from all countries should be aware that sharing information on nGM products will be vital, since global harmonisation of regulatory approaches towards applications of genome editing and other nGMs will not be easily achieved in the near future.

6.4 Challenges for harmonisation of regulatory approaches between legislations

Impacts on international trade result from the situation that different regulatory systems for biotechnology are operated side-by-side by different countries. The level of harmonisation between the existing biosafety frameworks regarding nGM-applications is limited. Differences in their approach to nGM-applications are apparent between most of the analysed regulatory frameworks, not just between systems with either process- or product-oriented triggers. Recent initiatives exist to modernize frameworks which were introduced several years ago, e.g. for the USA. Unfortunately the focus of this revisions will likely not be directed to harmonization, for example using the CPB as a forum (KUZMA 2016a).

Therefore similar issues have to be considered for nGM products as they have occurred for GMOs during the past years. This will result in a growing number of the following issues as:

- Different costs and time requirements for risk assessment in different countries, due to the different data requirements.

- Asynchronous authorization of similar products, e.g. due to the different timespans for authorisations to be granted in different systems.
- LLP situations involving nGM products non-authorised in importing countries.
- Increased challenges for border controls and inspections to enforce different regulatory requirements, including labelling requirements.

The lack of ability to identify some of the nGM applications by currently applied molecular analysis will likely create additional difficulties for legislations which implement provisions for labelling and traceability of regulated biotechnological products.

6.5 Challenges for the further development of regulatory frameworks with a view to nGM applications

The study identifies a number of serious challenges, which need to be considered in the framework of discussions how to regulate nGM applications.

Some of these difficulties are due to the wide range of different nGM applications. It consists of a whole spectrum of techniques which are used to establish nGM plants with different traits and characteristics. Some of these nGM applications are comparable to GM products regulated in the various countries. Some applications in particular genome editing applications to insert small sized, random genetic changes at specific genomic locations share similarities with products developed from naturally occurring wild relatives or by means of random mutagenesis, which are not consistently covered by GMO- or other biosafety legislation. A third group of nGMs, including applications directed to epigenetic engineering by RdDM or multiplexed applications of genome editing for simultaneous modification of a multitude of genetic targets, is associated with own regulatory challenges, which are not adequately addressed by the current regulatory frameworks (ECKERSTORFER et al. 2019b).

Also the available legislative options are not entirely well suited to address all of the apparent regulatory challenges and all types of biotechnology applications with similar appropriateness. Process-oriented regulatory frameworks are considered easier to implement for GMOs and have been successfully used for a long time by a considerable number of countries worldwide. However regulatory frameworks with a novelty-based product-oriented trigger are more flexible as regards the different nGM applications. Such systems will not require repeated revision to adapt the trigger definitions to the latest technological developments and also focus attention and resources to applications with a lacking history of safe use.

However, operating a process-oriented system for GMOs side by side with a product-oriented system for nGM applications does not appear to be an easily implementable option. Equally difficult to implement and disruptive for the existing process-oriented systems for GMO regulation would be a complete switch to a new regulatory system addressing all sorts of biotechnology applications, including GMOs and nGM applications. Such a step would be unprecedented, no such revisions of existing legal frameworks in any of the countries analysed was attempted.

A sole focus to achieve legal consistency, like the recent technical amendment of the Australian regulatory system or the ruling of the ECJ (ECJ 2018), does not sufficiently

address risk-oriented considerations and is thus not optimal from a risk assessment perspective. It is therefore necessary to further discuss all aspects related to a possible proposal for future policies towards the regulation of nGM applications and to continue to review the accumulating experience with regulation of nGM applications derived from different countries which are implementing different strategies.

7 Annex 1: Questionnaire used to conduct expert-interviews

Introductory question:

- How are you involved in the regulation and risk assessment of biotech products in your country?

Part 1

Trigger for regulation of biotech applications:

- Who is making decisions whether specific biotech application are subjected to existing regulations in regulatory practice?
- Which considerations are used to establish the regulatory status of applications? (in other words: What triggers regulatory oversight?)
  (is the trigger related to i) process of generation, ii) product-characteristics, iii) specific risk considerations or iv) a combination of different triggers?, Novelty?)
- Are risk-issues considered to establish the regulatory status? (How?)

Specific question for systems with product-oriented triggers

- Can you give examples, which applications are regulated or not?
  (e.g. is conventional HR regulated in your country and if so on what basis?
  (Which applications are additionally regulated/not regulated in comparison with the scope of regulation in EU/Cartagena Protocol?)
- Are decisions concerning regulation of biotech applications made public? (How?)

Regulatory proceedings:

- What is the remit of competent authorities for regulated products/organisms?
  (If more than one authority is involved: Cooperation between involved authorities?)
- How are the opinions of different involved authorities taken into account in overall decision making? May opinions be disregarded? Does that happen in practice?)
- Which procedure is implemented? (What are main steps in the regulatory pathway?)
- Which specific requirements apply to regulated applications?
  (notification time-limited) authorization/ – (renewal, risk assessment, risk management, monitoring)
- What goes well and what is difficult? Which requirements are easy or difficult to implement?

Regulatory environment:

- Which other general regulations apply to biotech applications?
  (What are the objectives of these regulations?)
- Who is responsible for implementation?
  (Cooperation between involved authorities?)
- What are the basic principles for regulation? (precautionary approach, liability law?)

- Is a further development of the regulatory framework in your country discussed currently? (Which issues/developments triggered these discussions and what is their focus?)

Part 2

Regulation of nGMs / Scope of regulation

- Which nGM applications are regulated and how are the mentioned examples of nGM applications regulated? (cf. list of techniques covered in the study)
  Are decisions based on general administrative provisions in existing legislation?
- Are specific regulations or existing regulations applied to regulate nGMs?
  (GMO regulations? other regulations? – e.g. for conventional breeding products)
- Are decisions based on the definition of GMOs in specific regulations?
  (Was this definition amended with a view to nGMs?)
- How is the definition of regulated items (GMOs) interpreted in practice?
  (e.g. as regards introduction of foreign DNA, new combinations of genetic information, intermediary transgenic modifications, somatic transgenic modifications (agroinfiltration, grafting),
- Will existing regulations cover application of emerging technologies or is there a specific range of covered applications?
  (Which? Examples - Genome editing e.g. without transgenic modification? Serial/multiplexed applications?)

Risk assessment approach:

- Is a risk assessment conducted for nGMs?
  (Is it a (mandatory) requirement for authorisation?)
- Which entity is subject to RA (“event”, variety)
- Which applications are exempted from RA?
- How is the RA conducted?
  Is a tiered system implemented – e.g. preliminary RA, comprehensive assessment (of specific issues)
  Do specific standards apply for some applications (different information elements, different information requirements?
- Which issues are considered during RA?
  (technology-oriented considerations? product-specific considerations? – How is “product” defined as regards RA? - GMO event/ variety)
- Are benefits considered during RA? (or otherwise, e.g. for decision-making?)
- Is there /Will there be an environmental monitoring for nGMs application and how is it designed?

Challenges for implementation:

- Which (specific) challenges are associated with the implementation of national regulations?

- What is done to address these challenges?
- What could be done to support implementation? (in principle? considering practice?)
- Is the ability to identify nGM products an issue?
- What approaches are used for identification?
- Are there efforts to establish new (specific) regulations or amend existing regulations? (Which ones? State of proceedings? Timeframe for coming into force?)
- Are international harmonisation issues discussed in your country with respect to nGM? As for example WTO compliance?
- How do you deal with imports from countries that do not regulate nGM?

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