CHAPTER 5

Regulatory framework of genome editing in Brazil and worldwide

Letícia Rios Vieira
Natália Chagas Freitas
Fernanda Justen
Vívian de Jesus Miranda
Bruno de Oliveira Garcia
Alexandre Lima Nepomuceno
Renata Fuganti-Pagliarini
Maria Sueli Soares Felipe
Hugo Bruno Correa Molinari
Edivaldo Domingues Velini
Eduardo Romano de Campos Pinto
Maria Lucia Zaidan Dagli
Galdino Andrade
Patricia Machado Bueno Fernandes
Liliane Marcia Mertz-Henning
Adilson Kenji Kobayashi

Introduction

The regulation of the use of products obtained through genome-editing techniques has been the subject of great debate worldwide. Currently, the discussions are mainly focused on whether products obtained by different strategies of site-directed nucleases (SDN) should or not be classified as Genetically Modified Organisms (GMOs).

In the SDN-1 application, the natural DNA cell repair pathway (Non-Homologous End-Joining - NHEJ) is explored to introduce simple random mutations (substitutions, insertions, and deletions) by systems such as CRISPR-Cas, TALENs, or Zinc Fingers Nucleases, which cause silencing of the gene product after breaking DNA (by Double-Strand Break - DSB).

In the SDN-2 approach, a template DNA is also used to introduce a change in the sequence of nitrogen bases (A, C, G, T) at the target site where the DSB occurred, exploring another natural repair system directed by a DNA fragment from the same species (Homology-Directed Repair - HDR).

In the SDN-3 approach, both NHEJ and HDR can be explored to insert one or more DNA fragments with sequences necessary for the expression of a gene (promoter, coding, and terminator region) at a specific location in the genome.

In the following topics, questions related to genome editing regulation in different countries are discussed in detail.

Regulation of gene editing in South America

Brazil

The total area in the world cultivated with genetically modified (GM) crops has increased a thousand times over the past two decades, from a few thousand hectares in 1996 to more than 190.4 Mha in 2019 (ISAAA, 2019). Among the countries producing transgenic crops, Brazil has the second-largest agricultural area, with more than 51.3 Mha, surpassed only by the USA, with 75 Mha. In the 2018/2019 crop season, over 95% of soybean fields were planted with GM cultivars; for corn, over 88% (first and second crop seasons), and for cotton, it reached over 84% of the total area (ISAAA, 2019).

Like many other plant breeding techniques, the use of GMOs in agriculture has become important for the production of food and plant by-products. However, unlike other technologies, the regulatory framework for GMOs is based on a broad list of requirements for risk assessment, which often differ from country to country. These requirements are primarily intended to protect human health, animal and environmental protection from possible adverse effects of the GMO. However, in many cases, such requirements are not proportional to the risks which results in a costly and time-consuming process. As an unintended outcome, due to the high costs of deregulation, only a few large multinational companies (currently BASF, Bayer, Corteva, and Syngenta) have adequate resources to deregulate new GM crops, whereas publicly funded research institutions, small and medium-sized companies, and universities are generally unable to develop a product that reaches the market. Even though they could benefit a broader range of stakeholders, particularly in poor regions, many socially beneficial technologies have been discontinued due to the regulatory limbo created by the GMO controversy.

However, after more than two decades of experience, without significant impact on human, animal, or environmental health, regulatory agencies are developing a more effective regulatory framework for emerging technologies, such as genome editing techniques and topical interfering RNA. Thus, allowing acceleration in the democratization of biotechnology in agriculture, making it more sustainable, guaranteeing food security, maintaining biosafety and economic, social, and environmental balance.

Brazilian legislation on GMOs

In Brazil, the Biosafety Law (Law No. 11,105, March 24, 2005) was an important regulatory mark establishing the safety norms and inspection mechanisms for activities involving GMOs and their by-products. This law, regulated by Decree No. 5.591, of November 22, 2005, was a comprehensive and complementary revision to a previous biosafety law (Law No. 8974, May 1, 1995), which was issued mainly to regulate the first commercial planting of glyphosate-resistant GM soybean in 1998. Besides determining the general rules for research and commercial activities with GMOs, the Biosafety Law regulates principles and establishes safety standards and mechanisms for monitoring activities involving GMOs and their by-products. The principles used to draft this law encouraged scientific advances in the areas of biosafety and biotechnology, life protection, human health, animal and plant health, as well as compliance with the precautionary principle for environmental protection. The Biosafety Law also established the National Biosafety Council (CNBS – in Portuguese *Conselho Nacional de Biossegurança*). In addition, as foreseen by the Biosafety Law, the National Technical Biosafety Commission (CTNBio – in Portuguese *Comissão Técnica National de Biossegurança*) was created to support the Federal Government in the establishment of the National Biosafety Policy. CTNBio is also responsible for issuing normative resolutions and instruction supporting the technological development of the sector with legal assurance and biosafety.

The objective and scope of the Biosafety Law is to provide safety standards and inspection mechanisms for construction, cultivation, production, handling, transportation, transfer, import, export, storage, research, environmental release, unloading, and commercialization of GMOs and their by-products. The law covers research activities and commercial uses of products developed for agriculture, human and animal health, the environment, and fishing. Anyone interested in carrying out one of these activities must request permission to CTNBio, which will respond within the deadline stipulated in the Normative Resolutions. All public and private organizations, national or foreign, that want to carry out activities or projects in Brazil, must request the Certificate of Quality in Biosafety (CQB - in Portuguese *Certificado de Qualidade em Biossegurança*) issued by CTNBio before starting any activity. CTNBio, through its Normative Resolutions, is responsible for establishing the biosafety guidelines for matters within its competence. Among its prerogatives, the law delegates to CTNBio the assessment of new technologies and their possible impacts on the environment, human and animal health in the country. If necessary, CTNBio may also propose regulations for these new technologies.

Regulation of new breeding technologies in Brazil

For any new technology, such as CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats), it is essential to guarantee its safety. However, to allow technological advancement, all safety requirements must be proportional to the risk. When the Biosafety Law was issued, most of the Innovative Precision Improvement Techniques (TIMP - in Portuguese *Técnicas Inovadoras de Melhoramento de Precisão*), also known as New Breeding Technologies (NBTs) were still at an early stage and, at the time, were not considered.

Thus, in 2015, CTNBio established a task force of experts among its members to analyze the products of the new breeding techniques and define how these products should be included in the definitions of the Biosafety Law, and propose improvements in the current regulations. The techniques analyzed by the task force included gene editing, early flowering, reverse breeding, interfering RNA, oligonucleotide-directed mutagenesis, among others. For most products and technologies considered by the task force, the use of NBTs can accelerate the introduction of traits of interest in elite genotypes in breeding programs. In many situations, the final product could be classified as non-genetically modified (non-GM) for legislation purposes.

Several products obtained by editing genes result in genetic modifications that could be obtained by established mutation techniques, such as radiation and chemical mutagenesis. As the Brazilian Biosafety Law considers organisms obtained by mutagenesis methods as non-GM, the task force considered that, after a case-by-case analysis, some products could be excluded from the scope of the legislation on GMOs. CTNBio Normative Resolution No. 16 (RN16), proposing an updated NBTs regulation, was drafted based on the report of the task force and regulations and experiences of other countries. The RN16 draft was unanimously approved by the members of CTNBio and by the Legal Counsel of the Ministry of Science, Technology, and Innovations, and published in the Federal Official Gazette on January 15, 2018.

In general terms, the principle of RN16 is to determine, through a case-by-case consultation system, whether a product generated by NBTs should or not be classified as GMO by CTNBio (Figure 1). For this consultation, the developer institution must provide information about the original organism and the product, including the methods used to generate it, and its molecular analysis. The classification of a product as non-GMO (for legislation purposes) is based on the following criteria: (I) absence of recombinant DNA/RNA; (II) presence of genetic elements that could be obtained by crossing; (III) presence of induced mutations that could also be obtained by established techniques, such as exposure to radiation or chemicals; and (IV) the presence of mutations that could occur naturally.

In practical terms, products obtained by random mutation directed to the site that involves the junction of non-homologous ends (SDN1 mutation) or homologous repair directed to the site that involves few nucleotides (SDN2 mutation) and that meet the conditions established in RN16, could be designated as non-GMO, in a case-by-case analysis. In contrast, transgene inserts targeted to the site (SDN3 mutation) will normally be classified as GMO, in a case-by-case analysis, according to the RN16. If the product is designated as GMO, the developer must comply with all biosafety requirements and will be approved only after CTNBio's risk assessment. If the product is not classified as a GMO, it can be registered using existing procedures.

RN16 applies to all types of organisms, including plants, animals, and microorganisms, in the research and/or commercial release phase.

Brazilian regulatory framework

The Biosafety Law established a structure with four main organizations responsible for risk assessment, and management (Figure 1): (1) National Biosafety Council (CNBS), (2) National Technical Biosafety Commission (CTNBio), (3) Local Biosafety Committee (in Portuguese *CIBio – Comissão Interna de Biossegurança*) and (4) Registration and Inspection Organizations and Entities (in Portuguese *OERF - Órgãos e Entidades de Registro e Fiscalização*), which includes the Ministry of Agriculture, Livestock and Supply (MAPA); the Ministry of Health (MS), the Ministry of the Environment (MMA), and the Secretariat of Aquaculture and Fisheries.

The Institutions that intend to work with GMOs must establish a Local Biosafety Committee (CIBio) and request a Certificate of Quality in Biosafety (CQB) to CTNBio. The CQB is issued after analysis by CTNBio that authorizes the institution to carry out activities with GMOs in its facilities, considering that the required safety standards are met. After the approval of the CQB, any demand for commercial activity with GMOs must be submitted to CTNBio by the CIBio's president of the institution. For a commercial release request, a complete and detailed dossier with all biosafety risk assessments must also be included in the process. The guidelines for risk assessment are established in Normative Resolution No. 24, of January 7, 2020, which provides the regulation for the commercial release of GMOs and their derivatives. CTNBio evaluates the risk and prepares a technical report. If the GMO is approved for commercial release, it is forwarded to CNBS.

National Biosafety Council (CNBS – *Conselho Nacional de Biossegurança*)

CNBS is a collegiate body composed of eleven high representatives of the State, including the Chief of Staff of the Presidency, who presides over it; Minister of

Justice; Minister of Science, Technology and Innovations; Minister of Agricultural Development; Minister of Agriculture, Livestock and Supply; Minister of Health; Minister of the Environment; Minister of Development, Industry and Foreign Trade; Minister of Foreign Affairs; Minister of Defense, and the Secretary of Aquaculture and Fisheries.

CNBS provides advisory assistance to the President of the Republic in the formulation and implementation of the National Biosafety Policy, establishing principles and guidelines that consider socio-economic and political conveniences, and opportunities of national interest involved in the commercial use of GMOs and related products. The CNBS technical opinion on a final decision to release a GMO for commercial use will only be requested if socio-economic and/or strategic policy decisions are required. Technical judgment on the biosafety of a commercially used GMO is under CTNBio's responsibility. However, CNBS has 30 days to refute the commercial approval of a GMO after CTNBio has released its official position. If the refutation does not occur within 30 days, the product is automatically authorized for sale.

National Technical Biosafety Commission (*Comissão Técnica Nacional de Biossegurança* - CTNBio)

CTNBio, linked to the Ministry of Science, Technology, and Innovations (MCTI – in Portuguese *Ministério da Ciência, Tecnologia e Inovações*), is a multidisciplinary advisory and deliberative collegiate that provides assistance and technical support to the federal government to formulate, update, and implement the National Biosafety Policy for the development of GMO products or biotechnology products that at some stage could generate a GMO. CTNBio also establishes technical safety standards regarding the authorization of activities related to research, and the commercial release of GMOs. In addition, CTNBio is responsible for zoo-sanitary, phytosanitary, human health, and environmental risks assessment of GMOs, and also establishes risk management measures. Other competencies of CTNBio include authorizing the importation of GMOs for research, providing technical assistance to registration and inspection organizations, and monitoring the development and technical-scientific progress achieved in biosafety, biotechnology, bioethics, and related areas, with the aim to increase the capacity of protecting human, animal and plant health, and the environment.

CTNBio is organized into permanent sectoral sub-commissions in the areas of plant and environment, human, and animal health. The president of CTNBio is appointed by the MCTI Minister for a 2-year term, extendable for the same period. CTNBio has a

permanent executive secretariat that provides technical and administrative assistance and organizes monthly meetings (except in January and July).

CTNBio consists of 27 full members and their substitutes, who are also appointed by the MCTI minister after receiving nominations from other Ministries. All members have a two-year term, renewable for two consecutive terms. They must be Brazilian citizens with recognized technical competence and outstanding participation in the scientific community. All members must have a doctorate, and be professionally active in the areas of biosafety, biotechnology, biology, microbiology, health and environment, human/animal health, or related areas. Twelve members of the scientific community are directly appointed by the MCTI, while the others are appointed by one of the bodies of the CNBS: Ministry of Agriculture, Livestock, and Supply; Ministry of Health; Ministry of the Environment; Ministry of Agricultural Development; Ministry of Development, Industry and Foreign Trade; Defense Ministry; Secretariat of Aquaculture and Fisheries; Ministry of Foreign Affairs, and Ministry of Justice. The complete list of CTNBio's members can be found on its website.

CTNBio meetings can be held with the 14-member quorum (half plus one), including at least one representative from each of the four subcommittees. If necessary, representatives of the scientific community, the public sector, and civil society entities with experience in a specific field may be invited to attend meetings, but they are not entitled to vote. Any decision taken by CTNBio must be approved by a majority vote. To provide greater transparency to the process, all decisions are published in the official journal and open for public comment within 30 days, in the same way, that all meetings are open to citizens, who can consult the agendas, as well as all documents produced by the commission, which are available on the CTNBio's website[1].

Local Biosafety Committee (*Comissão Interna de Biossegurança* - CIBio)

Any public or private institution that uses genetic engineering techniques and methods to develop biotechnological products, which at some stage of development can generate a GMO, must have a CIBio, composed of individuals with adequate training and education in the areas of biotechnology, genetic engineering, biosafety or other related fields. The Biosafety Quality Certificate, a document necessary for CIBio to work under government control, is also issued by CTNBio to the institution in question.

[1] Available at http://ctnbio.mctic.gov.br

As a mandatory procedure, a researcher must be appointed as responsible for each project involving GMOs in the institution. Also, each CIBio is legally responsible for ensuring the biosafety conditions of the entity's facilities, conducting regular inspections, and sending an annual report of its activities and projects to CTNBio. Currently, CTNBio supervises 480 public and private institutions in Brazil.

Registration and Inspection Organizations and Entities (Órgãos e Entidades de Registro e Fiscalização - OERF)

The OERF include the Ministry of Agriculture, Livestock, and Supply; Ministry of Health; Ministry of Environment, and Secretariat of Aquaculture and Fisheries.

Per Law No. 11,105 and within its field of competence, in compliance with CTNBio's resolutions and technical opinions, OERF is responsible for monitoring GMOs and their by-products. Its responsibilities include: (1) inspecting research activities, (2) registering and inspecting the commercial use of GMOs, (3) authorization to import products for research and commercial use, (4) maintaining up-to-date information on institutions and researchers who carry out activities and projects; (5) assist CTNBio in defining parameters for assessing biosafety; (6) disclosing to the public, grant registrations and authorizations for commercial use of GMOs; and (7) enforce the law and apply the penalties established when a non-compliance is identified.

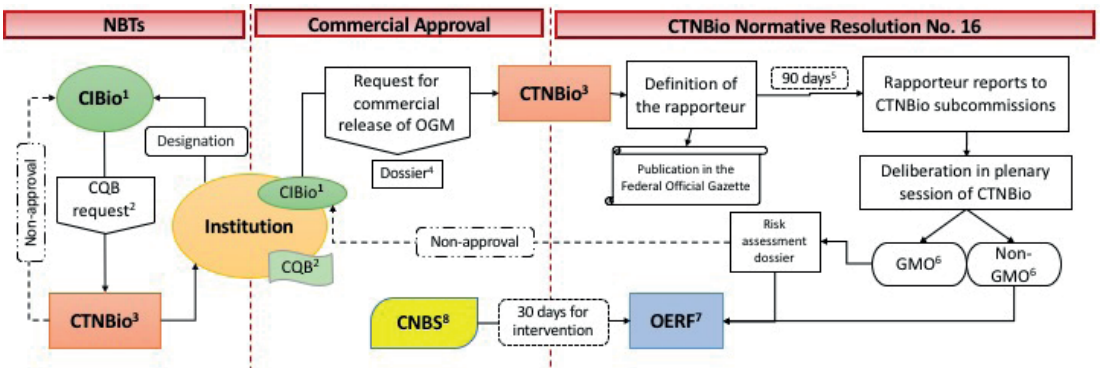

Figure 1. The workflow of the general process of approval and commercial release of products generated by NBT, according to the Brazilian Biosafety Law nº 11,105/2005 and Normative Resolution nº 16. Caption: 1) Local Biosafety Committee; 2) Biosafety Quality Certificate; 3) National Technical Commission on Biosafety; 4) Detailed dossier, with biosafety risk assessments; 5) Extendable for an equal period; 6) Genetically Modified Organism; 7) Registration and Inspection Organizations and Entities; 8) National Biosafety Council.

Overview of the status of biotechnology in Brazilian agriculture

Brazil is one of the main producers of agricultural goods in the world and one of the few countries that could considerably increase its production in the coming decades, without compromising environmentally protected areas, including the Amazon rainforest. In addition, Brazil also has great potential to become the main supplier of biofuels. Unlike most developed countries, where bioenergy production could compete with food production, Brazil could grow more than 30 Mha without destroying native and preserved environments or invading food production areas (Malingreau et al., 2012). Also, Brazil contains between 15% and 20% of global biodiversity, which has enormous potential as a source of new products for agriculture, medicine, and industry.

The Brazilian agriculture (from small to large farmers) and all the agribusiness related to it have all the conditions to increase their development at levels similar to those of other emerging economies and, consequently, help in the economic and social progress of the country contributing to feeding the growing world population. In the 1970s, the agricultural and livestock production flow to the Cerrado areas in the Midwest Region revealed how agribusiness can improve economic and social development. Some cities in the Midwest, for example, currently have the highest human development index in Brazil.

Many important achievements of Brazilian agriculture in recent decades resulted from the combined application of biotechnological and genetic improvement approaches. The combination of these methodologies is crucial to guarantee sustainable food production, in a scenario with multiple challenges resulting from climatic changes and a growing world population. Thus, to maintain productivity, it is essential to be alert, informed, and familiar with new technologies that could change concepts and paradigms of production and consumption.

In December 2018, CTNBio evaluated the first consultation on the commercial release of plants generated using NBTs in Brazil. A corn genotype in which the metabolic pathway for amylose production was knocked down by CRISPR/Cas9 was classified as non-GM. After analysis, CTNBio concluded that the mutation could have been obtained by conventional breeding methods or induced by other mutagens, such as ionizing radiation or by chemical agents. In this specific case, the reduction in amylose production resulted in almost 100% amylopectin content, which is interesting for some industrial uses of corn starch.

In another consultation, also in 2018, an edited yeast strain (*Saccharomyces cerevisiae*) called "Excellomol" with point polymorphisms introduced in specific genes was submitted. Excellomol increased the production of ethanol from

sugarcane. Such polymorphisms already occur naturally in the CBS 6412 strain of *S. cerevisiae*, originally identified in the production of sake. Since these mutations could have been introduced by other methods of mutagenesis the edited yeast was classified as non-GM.

Until March 2020, there were ten consultations since the approval of RN16. Five lines of microorganisms (*Saccharomyces cerevisiae*) for bioethanol production, hornless cow (for handling dairy cow), tilapia for improved fillet yield, waxy corn for starch quality, a vaccine for canine parvovirus control, and RNAi for the topical application to mosquito control. According to the provisions of the RN16, all these products, except the hornless cow, were considered by CTNBio as non-GMO. The development of NBTs evaluated by modern regulations that protect human and animal health and the environment will allow the democratization of biotechnology in Brazilian agribusiness. In this context, small, medium, and large national and international institutions could participate in the Brazilian and worldwide market, developing and introducing new solutions and products through a more sustainable approach without the controversy created about GMOs.

Argentina

Argentina was a pioneer country in the regulation of NBTs. In 2015, the Secretariat of Agriculture, Ganadería y Pesca (SAGyP) released the Resolution 173/15, which defines the assessment guidelines for NBT-derived crops. It is important to note that the resolution was drafted without the requirement of a list of specific technologies and is not restricted to the technical innovations available at the moment. As new breeding technologies are constantly published and patented, the inclusion of a specific list could compromise the speed of regulation of additional technological innovations.

The Comisión Nacional Asesora de Biotecnología Agropecuaria (Conabia) is the entity responsible for assessing, based on technical and scientific criteria, the potential environmental impact of the introduction of biotechnological crops in Argentine agriculture. The commission is recognized worldwide for its experience in the evaluation of dossiers, being considered as a reference center for the biosafety of GMOs by the Food and Agriculture Organization of the United Nations (FAO) (Ministerio de Agricultura, Ganadería y Pesca, 2019). Conabia has active participation in international debates related to biosafety and regulatory processes (USDA Foreign Agricultural Service, 2019). Therefore, Conabia is the body responsible for the evaluation and regulation of new breeding technologies, which guarantees compliance with the Resolution No. 173/15.

All products obtained by genome editing must be submitted to Conabia. The dossier can be submitted in two moments: after obtaining the final product or in the design phase of the creation process (project). In the design phase, inventors can consult Conabia to evaluate the expected product, determining whether the hypothetical product would be under GMO regulation or not. When the NBT-derived product is obtained, technical data on the genetic modification must be submitted to ascertain whether the expected regulatory status remains the same as preliminary assessment.

Under the regulatory framework, the evaluation time is 60 days, and electronic forms are available for speedy evaluation. The main criteria taken into account are (1) the techniques used in the process; (2) the new combination of the generated genetic material; and (3) the absence of a transgene in the final product. A genetic modification is considered a new combination of genetic material when a stable and permanent insertion of a gene(s) or DNA sequence(s) into the plant's genome is present. In such cases, the final product will be regulated as GMOs (Resolution 701/11 and 763/11). Also, even if a crop is exempt from GMO regulations but it has characteristics that pose a risk, it may undergo additional monitoring by the responsible authorities (Whelan; Lema, 2015).

Chile

In Chile, the *Servicio Agrícola y Ganadero* (SAG) is the entity responsible for regulating and monitoring the introduction, and propagation of genetically modified plants in the environment. An official SAG pronouncement in 2017 determined the regulatory procedure for crops obtained by NBTs, establishing a case-by-case approach, similar to Argentina. In general, crops developed using genome editing techniques that do not contain a new combination of genetic material are not subject to GMO regulations and are outside the scope of Resolution No. 1523/2001. For these purposes, a new combination of genetic material means a stable insertion of one or more genes or DNA sequences coding proteins, interference RNA, double-stranded RNA, signal peptides, or regulatory sequences (Whelan; Lema, 2019).

Individuals or legal entities, research centers, or universities interested in introducing a new crop obtained by NBTs into the Chilean territory must forward a request form to the SAG's Agricultural Protection and Forest Division. The assessment is carried out within 20 working days. The request form must contain technical information including the name of the species, the variety/lineage, the description of the phenotype obtained, the company or institution that developed the material, the methodology, and the characteristics of the biotechnological technique used

with the indication of the modified DNA sequences. Also, the applicant must inform whether the material has precedent for authorization in another country and if so, the official documentation must be presented. The SAG decision is valid for an indefinite period but can be canceled if new scientific discoveries are available.

Colombia

In Colombia, the technical control of production and commercialization of agricultural products is under responsibility of the *Instituto Colombiano Agropecuario* (ICA). In 2018, the Resolution 29299 was issued, which establishes the consultation guidelines for products obtained by NBTs, on a case-by-case basis. The procedure for determining whether a cultivar developed by NBT corresponds to a GMO or to a conventional organism takes into account the presence or absence of exogenous genetic material. According to the document text, a *cultivar* is designated as a generic name to refer to varieties, plant lines, hybrids, and clones used as planting materials. *Exogenous genetic material* corresponds to a gene, set of genes, DNA sequences, that are part of a genetic construction and were stably introduced into the genome, through modern biotechnology techniques, overcoming the natural physiological reproduction barriers. In this context, if a cultivar does not have exogenous DNA sequences, it is not classified as a GMO. and is free from the regulation proposed in Decree 4525/2005.

The request for evaluation of a product obtained by NBTs must be sent to ICA, which analyzes the documentation within 30 days. For this, the applicant must be registered with the ICA as a seed producer, seed importer, or plant breeding research unit. The documentation in the application covers the following technical-scientific information: (1) the taxonomic classification of the species; (2) methodology and genetic constructs used, including all genetic elements and, in the case of DNA-free editing, the protein and RNA sequences used; (3) the description of the generated phenotype; (4) alternative methodologies for generating the phenotype; (5) molecular characterization of the genetic modifications present in the improved cultivar compared to the original genotype and absence of exogenous material.

Paraguay

In Latin America, Paraguay was the fifth country to present its position and regulation about products obtained through NBTs. Resolution 565/2019 was sanctioned by the *Ministerio de Agricultura y Ganadería* (MAG), the competent

national authority in the agricultural and forestry sector. According to the resolution, the products are evaluated, on a case-by-case basis, by the *Comisión de Bioseguridad Agropecuaria y Forestal (Combio),* upon submission of the prior consultation form for products obtained by NBTs.

The prior consultation form consists of six sections covering information of the applicant, the organism, molecular biology, the phenotype, authorizations, and references. In the Information section about the applicant, the legal representative and technical responsible for the application must also be presented. The Organism section includes the scientific name and a detailed taxonomic description of the species, including cultivar and lineage must be provided. The Molecular Biology section refers to a detailed description of the technique used, and the steps applied, a molecular description of the target nucleotide sequences and their functions in the organism before and after the application of the technique. If applicable, the genetic construction with the details of the genetic elements, the analysis of target sequences, and, in cases where an intermediate transgene was used, the evidence proving the absence of recombinant sequences must also be provided. In the Phenotype section, examples of products with a similar phenotype on the market, the analysis of the probability of occurrence of other effects besides the desired phenotype, the expected changes in the proposed uses of the organism, and changes in the management recommendations of the resulting organisms are requested. In the Authorizations section, indicate if the organism has already been authorized by the regulatory entity from another country and if so, provide the type of authorization. Finally, in the References section, copies of all publications mentioned in the form must be included. Based on the assessment of all these points, Combio will determine whether the organism is classified as genetically modified or not.

Regulation of genome editing in North America

Canada

Canada differs from other countries in approving a genetically modified organism (GMO), the regulatory approach is based exclusively on products, and not on the process or technique used to develop the new product (Ellens et al., 2019). The product or the plant with a new characteristic (PNT – a plant with a novel trait) needs to present modification that differs from the original variety to be analyzed by

regulatory agencies. A PNT is a plant in which a characteristic has been introduced intentionally, new to plants of the same species grown in Canada, with the potential to affect the usage and safety of the plant considering the environment and human health (Canada, 2019). This rule applies to both plants developed by classical breeding and genetically edited plants.

Products created or modified in Canada are regulated by several government agencies, including the Canadian Food Inspection Agency (CFIA), Health Canada, and Environment and Climate Change Canada (ECCC). The CFIA is responsible for plant regulation, animal feed, fertilizers, and veterinary products of biotechnological origin. The Plant Biosafety Office of CFIA is responsible for coordinating the safety assessment of new foods. Health Canada supervises food, medicine, and pest control products. The evaluations conducted by CFIA and Health Canada are based on scientific criteria and guidelines established by the World Health Organization (WHO), the Food and Agriculture Organization (FAO), and the Organization for Economic Cooperation and Development (OECD) (Dederer; Hamburger, 2019). ECCC operates on the regulation of all animal products of biotechnological origin not covered by another federal law and is based on the Canadian Environmental Protection Act, 1999 (CEPA).

In order to receive registration approval and be able to enter the Canadian market, a product with a new feature needs to undergo several tests carried out by technicians from CFIA and Health Canada. These tests aim to corroborate the results already provided by the applicant. After reviewing all the data provided by the applicant coupled with the new tests, if all conditions are met, the product is accepted.

In Canada, when GM crops were being developed in the early 1990s, regulatory systems were also in development. Thus, the laws were already available to the needs of these crops. There is no specific law for plants genetically modified by NBTs or conventional breeding. The regulation is based on the product, which is released for consumption based on its safety assessment.

Four legislation acts are involved in the regulation of agricultural products. The Seed Act regulates stability, and environmental risk, for example, plant potential to become a weed and the impact of a plant or its products on non-target species (Branch, 2019a). The Animal Feeding Act regulates risks related to toxicity, allergenicity, and digestibility (Branch, 2019b). The Food and Drug Act establishes the risk limits for toxicity, allergenicity, metabolism, and nutrition-related to human consumption (Branch, 2020). In addition, CFIA applies the following guidelines to analyze herbicide-resistant varieties, regardless of the technology used to create a variety:

- Directive 94-08: Assessment Criteria for Determining Environmental Safety of Plants with Novel Traits.
- Directive 95-03: Guidelines for the Assessment of Novel Feeds: Plant Sources.
- Directive 96-13: Import Requirements for Plants with Novel Traits, including Transgenic Plants and their Viable Plant Parts.
- Directive 2000-07: Conducting Confined Research Field Trials of Plants with Novel Traits in Canada.

The International Service for the Acquisition of Agri-Biotech Applications (ISAAA) reported in 2017 that Canada planted an area of 13.12 million hectares with biotechnological crops, accounting for 7% of the world planted area. During the 21 years of commercialization of GM plants, Canada made a profit of US$8 billion (ISAAA, 2017), and with the new cultivars that are expected to be incorporated, increased profits in the coming years.

United States of America

In the United States of America, the regulation of crops produced through the use of genetic technologies is based on decades-old policies managed by various statutes and regulations, implemented by different federal government agencies (Dederer; Hamburger, 2019). American regulatory entities are the US Department of Agriculture (USDA), the Environmental Protection Agency (EPA), and the Food and Drug Administration (FDA). These federal agencies aim to ensure that genetically modified crops and their products are safe for health, the environment, and agriculture.

The regulatory policy for biotechnological products was established with the Biotechnology Regulatory Framework, published in 1986 (OSTP, 1986), and later updated in 1992. This document allows three conclusions that influence American biotechnology policy to this day: products are not necessarily different from conventional products; regulations should not focus on the process but the product, and regulatory jurisdiction must be based on use.

The Animal and Plant Health Inspection Service (APHIS) and the USDA Biotechnology Regulatory Service (BRS) are responsible for releasing field tests, interstate movement, and import of GM plants that may present some risk (Dederer; Hamburger, 2019). APHIS has released a new regulation, the Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient Rule (SECURE Rule) (United States, 2020),

which aims to update and modernize the Plant Protection Act, removing outdated processes, and inserting biotechnological regulations (United States, 2020a).

The EPA regulates GM plants with pesticidal substances under the Federal Insecticides, Fungicides, and Rodenticides Act (FIFRA) (United States, 2020b) and pesticide residues in GE foods under the Food, Drug, and Cosmetics Act (FDCA) (United States, 1938).

The FDA regulates food safety under the FDCA. In the USA, new food developers are legally responsible for assessing food safety and complying with FDA regulations and statutes. And to ensure food safety, the FDA relies on legal provisions that prohibit adulteration, and incorrect food identification (Dederer; Hamburger, 2019). A food is considered adulterated if it has or contains one or more substances added that could be harmful to health or if the additive is not safe. Thus, if GM or processed foods do not show nutritional differences from conventional food, it is considered equivalent. According to the FDCA definition, substances that are "generally recognized as safe" (GRAS) are excluded from food additives. Due to new forms of breeding and gene editing, several discussions have pointed to possible changes in the regulations.

The American government has always encouraged the use of new technologies in agriculture as a way to increase its competitiveness (Bergeson, 2017) and, currently, the use of genome editing techniques in plants is on the rise. In 2019, the USA planted 75 Mha of transgenic crops, which corresponds to 40% of the world total, which was 190.4 Mha (ISAAA, 2019), and are the leaders in approving and cultivating genetically modified varieties.

Regulation of genome editing in the European Union

The European Union (EU) has the strictest legislation in the world regarding the cultivation and consumption of GMOs in its territory with less than 0.1% of the global area is grown with GM crops Davison; Ammann, 2017). Only a single transgenic *Bt* event (MON810) is currently authorized for commercial cultivation in Spain and Portugal. However, the EU is a major importer of transgenic soybean and corn for animal feed (Dederer; Hamburger, 2019).

The EU regulatory concept strictly follows the "Precautionary Principle", which considers that, if an action may cause irreversible public or environmental damage, in the absence of irrefutable scientific consensus, the burden of proof is on the side of those who intend to practice the act or action that may cause the damage. Different GM crops would be within this principle, since they were manipulated

in the laboratory, and would be different from the original crops. In the EU, the regulation banning GMOs is well established, however, with the advancement of genetics, especially the NBTs, the discussion on the use of biotechnology in agriculture is resuming.

The EU regulation on GMOs is based on Directive 2001/18/EC; Regulations (EC) No. 1829/2003 and No. 1830/2003; in Regulation (EC) No. 1946/2003; in Directive 2009/41/EC and Directive (EU) 2015/412 (European Commission, 2020).

Directive 2001/18/EC regulates the assessment of environmental risks and the release of GMOs, as well as their commercialization (import, processing, and transformation) within the European bloc. The concept of GMOs for EU, according to this legal classification, is: "'genetically modified organism (GMO)" means an organism, except for human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination". This concept does not apply to human beings. According to Annexes 1A and 1B of that directive, genetic modifications without the use of recombinant DNA, and obtained by in vitro fertilization techniques, natural processes such as conjugation, transduction, transformation, polyploidy induction, classical mutagenesis (chemical mutagenesis and radiation), and protoplast fusion are excluded from the classification of GMOs.

Gene editing via CRISPR does not normally involve transgenics - the transfer of "genes" between species. However, on July 25, 2018, the EU Court of Justice (EUCJ) determined that all plants obtained through gene editing must be considered GMOs and fall within the scope of Directive 2001/18/EC (Ruffell, 2018). Among the justifications presented by the court, is the fact that the mutations caused by these techniques constitute changes made to the genetic material of the organism in an "unnatural" way and that the process uses recombinant DNA techniques. This is an aspect of EU regulation that differs from US and Canadian standards, based on product safety, regardless of the process used to obtain it (Friedrichs et al., 2019; Leone, 2019).

The precautionary principle for new approaches was used as a justification for the prohibition, aiming to avoid possible harmful effects to human, animal health, and the environment. Most requests for GMOs in the EU have been denied, and those approved have limited consent for 10 years (renewable), with mandatory monitoring after placing on the market (Schulman et al., 2020). The average approval time for food for human and animal consumption (excluding cultivation purposes) could take around 5 years (Zimny et al., 2019).

Considering the European community's concern with GM food and animal feed, Regulation (EC) No. 1829/2003 restricts the unauthorized entry of GMOs into the EU and obliges suppliers of GM plants, and products to label food containing more than 0.9% of GMOs, informing the methods for its detection (Davison; Ammann, 2017). Regulation (EC) 1830/2003 of the European Parliament and the EU Council also regulates the traceability and labeling of GM foods, to ensure that consumers are informed about the presence of GMOs and their products, to allow an informed choice of the product (Davison; Ammann, 2017). Besides Directive 2001/18/EC, which requires mandatory monitoring after the commercial release of GM products, Directive 2009/41/EC complements and requires EU-Member to send a report every three years, describing their experiences with the released product, informing risk assessment, accidents, an inspection of compliance control, consultation and information to the public, and waste disposal (European Commission, 2012). Besides these measures, through regulation (EC) No. 1946/2003, about transboundary movements of GMOs, it became mandatory to introduce protective measures in the border areas of the territory, to avoid possible contamination between non-GM and GM crops neighboring countries (European Commission, 2020).

Even with all these regulations, there were cases of release of the entry of GMOs into the European bloc, contrary to the opinion of several EU-Member. Faced with this setback, Directive (EU) 2015/412 of March 11 (which amended Directive 2001/18/EC) emerged, which concerns the possibility for the Member States to restrict or prohibit the cultivation of GMOs in their territory using the "opt-out" clause, and the principle of subsidiarity (Davison; Ammann, 2017). Among the Member States that have chosen to completely restrict the entry of GMOs into their territory are Austria, the Walloon Region (Belgium), Bulgaria, Croatia, Cyprus, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Slovenia, Northern Ireland, Wales, and Scotland (United Kingdom) (Friedrichs et al., 2019). Plants edited by the new breeding techniques are considered GMOs by the European parliament and are therefore included in all EU GMO regulatory measures.

EU legislation that restricts GMOs and crops grown in Europe has significant economic impacts on the food sector, and agriculture. The EU seed market, for example, is estimated at €7 billion a year (Friedrichs et al., 2019). The impossibility of cultivating, and developing crops improved by modern biotechnology also causes the transfer of research investments outside the EU, impacting the research and innovation sector.

According to Brookes and Barfoott (2014), in the 17 years (before 2012) of the adoption of agricultural biotechnology by 17.3 million farmers, there was an economic benefit of US$ 116.6 billion, which increased to US$ 167.7 billion by

2015. GM crops generated a 37% reduction in the use of chemical pesticides, a 22% increase in agricultural production, and a 68% profit for farmers (Klümper; Qaim, 2014). Similar or greater benefits can be achieved in the EU, through adherence to edited crops, besides the benefits of using green technology, including the European bloc in the competitive global commodities market. Among the EU's agricultural challenges is the sustainable production of food with fewer crop protection products, irrigation, grown in a smaller area, under constant climate change. These requirements show the need for new improved cultivars, leaving genome editing as a promising solution for the European market. However, the EU needs to harmonize its biotechnology legislation with other countries, mainly with the main food producers in the world.

Regulation of genome editing in Asia

China strictly regulates the import and production of GMOs, according to the regulations issued by the Chinese Ministry of Agriculture and Rural Affairs (MARA) in 2001, which predicts the administration of the security of agricultural GMOs. In 2018, through the National Bio-Safety Committee (NBC), MARA amended the regulations on safety assessment, import approval, and GMO labeling. The revised rules impose additional tests and studies in the country on biotechnological products. The Chinese government, as of 2016, created a 5-year support plan for research initiatives aimed at gene editing (Cohen, 2019). The purchase of Syngenta by state-owned ChemChina in 2017 reinforces China's interest in the field of technology for food production. Despite being one of the countries with the largest number of publications related to gene editing, the legislation classifies edited organisms as GMOs. MARA indicated in 2019 that new regulations are under development, to align China with other countries, as these regulations may provide a simplified regulatory process for genetically edited products in the future (United States, 2019).

In Japan, products edited using NBTs are evaluated on a case-by-case basis and need to be notified to the government, which requires technical information about the technique used and the genes targeted for modification. Modified organisms that contain exogenous DNA in their construction or are under the regulations for GMOs, as well as edited cultivars that might cross with an unedited cultivar, must be notified (Sato, 2020). Regulation is carried out by four Ministries: Ministry of Agriculture, Forestry and Fisheries; Ministry of Environment; Ministry of Education, Culture, Sports, Science and Technology; Ministry of Health, Labor and Welfare. In

addition, an independent commission, the Food Safety Commission (FSC), carries out the risk assessment of food and animal feed.

Recently, India issued preliminary rules for the regulation of edited products, requiring safety tests that prove the effectiveness of gene editing. Like many other countries, India adopts a position that evaluates the process used for editing instead of evaluating the final product. For SDN-1 technique regulation, extensive data demonstrating that the gene edition was successful, is required. When using SDN-2 for editing organisms, besides proving the effectiveness of the edition, field tests are necessary to prove the efficiency of the transformation. When inserting an exogenous DNA using the SDN-3 technique, the organism follows the same process as GMOs, which include tests for human and animal food safety, and risks to the environment. The responsibility for carrying out the evaluations lies with the Institutional Biosafety Committee, the Genetic Engineering Evaluation Committee, and the Genetic Engineering Review Committee (India, 2020).

Indonesia does not have specific regulations for the production of edited cultivars. All products from gene editing are evaluated as GMOs. The assessments and regulations are carried out based on the Protocol on Biosafety of the Convention on Biological Diversity, based on the Government Regulation No. 21/2005. The responsibility for the initial assessment is under the responsibility of a non-departmental government agency. Subsequently, the analysis is sent to the Convention on Biological Diversity (CBD), a biosafety commission linked to the National Agency for Drug and Food Control (Badan POM). If the product meets the regulations stipulated by law, it is forwarded to the National Agency for the Control of Medicines and Food, and the notification is then reassessed by the biosafety committee, and released (Badan Pengawas Obat dan Makanan, 2012).

Regulation of genome editing in Oceania

Australia

Australia adopts a position that evaluates the process used for editing instead of evaluating the final product. Organisms resulting from a gene-editing process are regulated by the Gene Technology Regulator (GTR). GTR is responsible for regulating the production and release of GMOs, based on the standards described in the Gene Technology Regulations 2001, made under the Genetic Technology Act 2000.

With the NBTs, such as CRISPR, transcription activator-like effector nucleases (TALENs), and Zinc-finger nucleases (ZFNs), the regulatory process needed to be adapted. In 2019, the Gene Technology Amendment (2019 Measures No. 1) was created. The NBT-derived product is systematically reviewed to determine whether it should or not be classified as a low-risk transformation or transformation exempt from notification. The regulations are described in sections 140 and 141 of the amendment. Item 4 of Annex 1 of the amendment states that organisms modified with NBTs are not considered GMOs since no nucleic acid is present. SDN-1 is not regulated due to similarity to traditional mutagenesis techniques. SDN-2 and SDN-3 may or may not insert an exogenous DNA into the organism's genome with stable or transient character (Eckerstorfer et al., 2019).

As the regulation of organisms modified by NBTs is the responsibility of the GTR, in Australia and New Zealand food is regulated by a joint system, the Food Standards Australia New Zealand (FSANZ). FSANZ is responsible to develop and define pre-market regulations, such as food labeling from gene editing (Food Standards Australia New Zealand, 2019).

New Zealand

New Zealand, unlike Australia, considers all gene-editing techniques as GMOs. The country adopts a position of caution and observance of the regulations stipulated globally, to adapt its system over time, according to international developments (Fritsche et al., 2018).

Research involving genetically edited plants is supervised by the Environmental Protection Authority (EPA), which is responsible for supervising the development, and release of GMOs under the Hazardous Substances and New Organisms (HSNO) Act 1996. All gene-editing techniques are regulated, even when exogenous genes are not incorporated (New Zealand, 2019).

Harmonization of global legislation on genome editing in plants

In the Brazilian evaluation (similar to what to other countries in the Americas, Japan, Australia, Israel, among others), mutations produced by SDN-1 are not classified as GMO in the light of Biosafety Law. The same occurs with products obtained by classical improvement, or by mutations induced by various external

factors, such as exposure to UV light, ionizing radiation, chemical substances, or even errors during DNA replication. The accumulated knowledge on the genome of different species has allowed a more precise modification when compared to traditional mutation systems as radiation or chemical agents used in the development of commercial varieties for decades.

Genome editing systems type SDN-2 may or may not be classified as GMOs under the Brazilian legislation and most countries in the Americas, in case-by-case analyses. SDN-2 is similar to natural mutagenesis, altering small portions of genomic DNA, as occurs in genetic improvement programs, or changes caused by chemicals/radiation, or even in the natural differentiation of germplasm from a species collected in different locations. The main differentiating factor in considering products obtained by the SDN-2 system as GMOs has been the presence of DNA of another species in the final product.

SDN-3 system, on the other hand, due to the complexity of the introduced genetic elements, normally is classified as GMOs, always depending on a case-by-case analysis, and the origin of the DNA used.

Unlike the Brazilian Biosafety Law, which excludes mutagenesis from the scope of GMOs, the decision of the Court of Justice of the European Union on the subject (case C-528/16, of July 25, 2018) established that Directive 2001/18/CE, on GMO risk analysis, applies to products obtained by "new mutagenesis techniques", that is, SDN systems.

The European scientific community, as well as companies that develop products with biotechnological techniques, has provoked a discussion with European regulatory agencies, aiming to review this decision and align European legislation with the rest of the world. In this sense, the European Food Safety Authority (EFSA), in a public consultation carried out in May 2020, evaluated the possibility of products obtained by SDN-1 and SDN-2 systems having a different risk analysis than what currently occurs in the European Union in the relation to GMOs. In a first discussion panel, EFSA had concluded that risk assessment methodologies on SDN-3 system could be simplified compared to what is done with GMOs, since in the SDN-3 system the introgression in the of gene sequences into the genome occurs in a targeted manner and defined place, unlike processes with traditional transgenics, in which insertions in the genome are random.

In a second discussion panel, the EFSA also decided that the conclusions of the first panel would be partially applicable to the SDN-1 and SDN-2 systems. Since SDN-1/SDN-2 approaches aim to modify an endogenous DNA sequence whose

final product does not contain exogenous DNA. Therefore, these products would not present any of the potential risks related to the insertion of a transgene.

Several countries, including Brazil, understand that the introduction of variability in species of economic importance could help achieve important sustainability goals, healthier foods, less use of chemical pesticides, contributing to a healthier environment, and mitigation of problems caused by global climate change, among other possibilities. However, innovations in genetics must take into account the basic principles of biosafety.

Legislation should not stop technological development and the possibility of generating biotechnology-based should not be restricted to a few institutions and companies, as occurred in the case of transgenics, considering the expensive and time-consuming approval processes created by each country. If products resulting from targeted mutagenesis, mainly SDN-1 and SDN-2 systems, are subject to the same risk assessment requirements as traditional GMOs/SDN-3, technological development may be restricted to few large companies, limiting competition and market share.

Brazil, Argentina, Canada, Chile, Colombia, USA are among the first to have legislation that regulates the use of gene editing techniques. In these countries, the increase in number, type, and size of institutions/companies developing products of interest to society, is clear. Moreover, there is a significant increase in the number of species worked with NBTs. In GMOs, investment was only viable for major commodities, such as soybeans, corn, and cotton, among the main ones.

As SDN-1 and SDN-2 systems simulate/imitate mechanisms of genetic variability induction that occur constantly and frequently in nature, their detection in genome-edited products is practically impossible. The European Union, in the report "Detection of food and plant foods obtained by new mutagenesis techniques" (European Commission, 2019), recognizes that products whose genome has been edited may be indistinguishable from products altered by natural processes or by conventional reproductive techniques.

Brazil, in alignment with the national and international scientific community, and with the legislation of several countries, many of which are commercial partners, understands the importance of harmonizing the biosafety laws of food exporting and importing countries. Biosafety laws should reflect and welcome technological progress, maintaining food quality and safety but also allowing diversification of participants in the production chain. Products generated by genome editing, mainly by the SDN-1 and SDN-2 systems, should not be subject to risk analysis

requirements like GMOs if they could also be obtained by conventional methods or spontaneous processes in nature.

Harmonization of regulatory rules also allows creating legal assurance for developers in each country, avoiding individual national/regional rules for products resulting from conventional random mutagenesis or the use of SDN systems. Also, it prevents two indistinguishable products from being regulated in two different ways.

References

ARGENTINA. Resolución 173/2015, 12 de mayo de 2015. **Secretaría de Agricultura, Ganadería y Pesca (SAGyP)**. Available at: https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-173-2015-246978/texto. Accessed on: 15 May 2020.

ARGENTINA. Resolución 701/2011, de 27 de octubre de 2011. **Secretaría de Agricultura, Ganadería y Pesca (SAGyP)**. Available at: https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-701-2011-189067/texto. Accessed on: 17 May 2020.

ARGENTINA. Resolución 763/2011, de 17 de agosto de 2011. **Ministerio de Agricultura, Ganadería y Pesca**. Available at: https://www.argentina.gob.ar/normativa/nacional/resoluci%C3%B3n-763-2011-185806/texto. Accessed on: 17 May 2020.

BADAN PENGAWAS OBAT DAN MAKANAN (Indonesia). **Peraturan nomor HK.03.1.23.03.12.1563 Tahun 2012.** Pedoman pengkajian keamanan pangan produk rekayasa genetik. 2012. Available at: https://standarpangan.pom.go.id/dokumen/peraturan/2012/Perka_BPOM_No_HK.03.1.23.03.12.1563_Tahun_2012_tentang_Keamanan_Pangan_PRG.pdf. Accessed on: 6 Out 2020.

BERGESON, L. L. Enlisting modern technologies to ensure a safe food supply. **Natural Resources & Environment**, v. 31, n. 3, p .31-34, 2017.

BRANCH, L. S. **Consolidated federal laws of Canada, Feeds Act.** 2019b. Available at: https://laws-lois.justice.gc.ca/eng/acts/F-9/. Accessed on: 20 May 2020.

BRANCH, L. S. **Consolidated federal laws of Canada, Food and Drugs Act.** 2020. Available at: : https://laws.justice.gc.ca/eng/acts/F-27/. Accessed on: 20 May 2020.

BRANCH, L. S. **Consolidated federal laws of Canada, Seeds Act.** 2019a. Available at: https://laws-lois.justice.gc.ca/eng/acts/S-8/. Accessed on: 20 May 2020.

BRASIL. Lei Nº 11,105, de 24 de março de 2005. Regulamenta os incisos II, IV e V do § 1º do art. 225 da Constituição Federal. Regulamenta os incisos II, IV e V do § 1º do art. 225 da Constituição Federal, estabelece normas de segurança e mecanismos de fiscalização de atividades que envolvam organismos geneticamente modificados – OGM e seus derivados, cria o Conselho Nacional de Biossegurança – CNBS, reestrutura a Comissão Técnica Nacional de Biossegurança – CTNBio, dispõe sobre a Política Nacional de Biossegurança – PNB, revoga a Lei nº 8.974, de 5 de janeiro de 1995, e a Medida Provisória nº 2.191-9, de 23 de agosto de 2001, e os arts. 5º, 6º, 7º, 8º, 9º, 10 e 16 da Lei nº 10.814, de 15 de dezembro de 2003, e dá outras providências. **Diário Oficial**

da União, 28 de março, de 2005. p. 1. Available at: http://www.planalto.gov.br/ccivil_03/_ato2004-2006/2005/lei/l11105.htm. Accessed on: 3 Set 2020.

BRASIL. Resolução Normativa Nº 16, de 15 de janeiro de 2018. Estabelece os requisitos técnicos para apresentação de consulta à CTNBio sobre as Técnicas Inovadoras de Melhoramento de Precisão. **[Comissão Técnica Nacional de Biossegurança – CTNBio]**. Available at: http://ctnbio.mctic.gov.br/resolucoes-normativas/-/asset_publisher/OgW431Rs9dQ6/content/resolucao-normativa-n%C2%BA-16-de-15-de-janeiro-de-2018?redirect=http%3A%2F%2Fctnbio.mctic.gov.br%2Fresolucoes-normativas%3Fp_p_id%3D101_INSTANCE_OgW431Rs9dQ6%26p_p_lifecycle%3D0%26p_p_state%3Dnormal%26p_p_mode%3Dview%26p_p_col_id%3Dcolumn-2%26p_p_col_count%3D3. Accessed on: 3 Set 2020.

BROOKES, G.; BARFOOT, P. Economic impact of GM crops: the global income and production effects 1996–2012. **GM Crops & Food**, v. 5, n. 1, p. 65-75, 2014.

CANADA. Canadian Food Inspection Agency. **Directive Dir 2000-07: Conducting Confined Research Field Trials of Plants with Novel Traits in Canada**. 2019. Available at: https://www.inspection.gc.ca/plant-health/plants-with-novel-traits/applicants/directive-dir-2000-07/eng/1304474667559/1304474738697#a1_1. Accessed on: 19 May 2020.

CHILE. Resolución N° 1.523/2001, de 6 de julho de 2001**. Servicio Agrícola y Ganadero (SAG)**. Available at: http://www.sag.cl/sites/default/files/RES_1523_2001.pdf. Accessed on: 17 May 2020.

COHEN, J. "Fields of dreams"**. Science**, v. 365, n. 6452, p. 422-425, 2019.

COLÔMBIA. Decreto N° 4525, de 6 de diciembre de 2005. **Ministerio de Agricultura y Desarrollo Rural**. Available at: https://www.ica.gov.co/getattachment/6ea8d6c3-aadc-42ad-958d-2eb377cfe528/2005D4525.aspx. Accessed on: 15 may 2020.

COLÔMBIA. Resolución N° 00029299, de 1 de agosto de 2018. **Instituto Colombiano Agropecuario (ICA)**. Available at: https://www.ica.gov.co/getattachment/2d02cc52-d1c5-4123-8a5a-aea9ad2ce926/2018R29299.aspx. Accessed on: 15 May 2020.

EUROPEAN COMMISSION. **Report on the experience of Member States with Directive 2009/41/EC of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (recast) for the period 2006 – 2009.** Brussels, 2012. 10 p. Available at: https://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:52012DC0398&from=EN. Accessed on: 2 Set 2020.

DAVISON, J.; AMMANN, K. New GMO regulations for old: Determining a new future for EU crop biotechnology. **GM Crops & Food**, v. 8, n. 1, p. 13-34, 2017.

DEDERER, H.-G.; HAMBURGER, D. (Eds.). **Regulation of Genome Editing in Plant Biotechnology: A Comparative Analysis of Regulatory Frameworks of Selected Countries and the EU**. Cham: Springer International Publishing, 2019.

ECKERSTORFER MF, ENGELHARD M, HEISSENBERGER A, SIMON S, TEICHMANN H. Plants Developed by New Genetic Modification Techniques-Comparison of Existing Regulatory Frameworks in the EU and Non-EU Countries. **Frontiers in Bioengineering and Biotechnology**. v. 7, 2019.

ELLENS, K. W.; LEVAC, D.; PEARSON, C.; SAVOIE, A.; STRAND, N.; LOUTER, J.; TIBELIUS, C. Canadian regulatory aspects of gene editing technologies. **Transgenic Research**, v. 28, n. S2, p. 165-168, 2019.

UNITED STATES. Department of Agriculture. **Animal and Plant Health Inspection Service**: Rules and Regulations. 7 CFR Parts 330, 340 and 372. Federal Register, v. 85, n. 96, 18 May 2020. Available at: https://www.aphis.usda.gov/brs/fedregister/BRS_2020518.pdf. Accessed on: on: 7 Jun 2020.

UNITED STATES. Department of Agriculture. Animal and Plant Health Inspection Service. **USDA SECURE Rule Paves Way for Agricultural Innovation**. Washington DC, 2020a. Available at: https://www.aphis.usda.gov/aphis/newsroom/news/sa_by_date/sa-2020/secure. Accessed on: 7 Jun. 2020.

UNITED STATES. Environmental Protection Agency. **Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) and Federal Facilities.** Policies and Guidance. 2020b. Available at: https://www.epa.gov/enforcement/federal-insecticide-fungicide-and-rodenticide-act-fifra-and-federal-facilities. Accessed on: 20 May 2020.

UNITED STATES. Foreign Agricultural Service. **China** - Peoples Republic of Agricultural Biotechnology Annual. 2019. 22 p. CH 18085. Available at: https://gain.fas.usda.gov/Recent GAIN Publications/Agricultural Biotechnology Annual_Beijing_China - Peoples Republic of_2-22-2019.pdf. Accessed on: 25 Aug 2020.

UNITED STATES. Office Of The Law Revision Counsel. **Federal Food, Drug, And Cosmetic Act.** Title 21 – Food and Drugs, chapter 9 – Federal Food, Drug, And Cosmetic Act. June 25, 1938, ch. 675, §1, 52 Stat. 1040. Available at: https://uscode.house.gov/browse/prelim@title21/chapter27&edition=prelim. Accessed on: 20 May 2020.

EUROPEAN COMMISSION. **GMO Legislation**. Available at: https://ec.europa.eu/food/plant/gmo/legislation_en. Accessed on: 11 Apr 2020.

FOOD STANDARDS AUSTRALIA NEW ZEALAND. **Review of food derived using new breeding techniques**: Final report. c2019. Available at: https://www.foodstandards.gov.au/media/Pages/Final-Report---Review-of-food-derived-using-new-breeding-techniques.aspx. Accessed on: 2 Set 2020.

FRIEDRICHS, S.; TAKASU, Y.; KEARNS, P.; DAGALLIER, B.; OSHIMA, R.; SCHOFIELD, J.; MOREDDU, C. An overview of regulatory approaches to genome editing in agriculture. **Biotechnology Research and Innovation**, v. 3, n. 2, p. 208-220, 2019.

FRITSCHE, S.; POOVAIAH, C.; MACRAE, E.; THORLBY, G. A New Zealand perspective on the application and regulation of gene editing**. Frontiers in Plant Science**, v. 9, p. 1-8, Sep., 2018.

INDIA. Ministry of science & technology. Department of Biotechnology. **Draft Document on Genome Edited Organisms**: Regulatory Framework and Guidelines for Risk Assessment. 2020. Available at: http://dbtindia.gov.in/sites/default/files/Draft_Regulatory_Framework_Genome_Editing_9jan2020a.pdf. Accessed on: 2 Set 2020.

ISAAA. **Global Status of Commercialized Biotech/GM Crops: 2019**ISAAA: Ithaca 2019. (ISAAA Brief, 53). Available at: https://www.isaaa.org/resources/publications/briefs/55/. Accessed on: 19 May 2020.

KLÜMPER, W.; QAIM, M. A meta-analysis of the impacts of genetically modified crops. **PloS One**, v. 9, n. 11, 2014.

LEONE, L. Gene Editing for the EU Agrifood: Risks and Promises in Science Regulation. **European Journal of Risk Regulation**, v. 10, n. 4, p. 766-780, 2019.

MALINGREAU, J. P.; EVA, H. D.; DE MIRANDA, E. E. Brazilian Amazon: a significant five-year drop-in deforestation rates but figures are on the rise again. **Ambio**, v. 4, n. 3, p. 309-314, 2012.

MINISTERIO DE AGRICULTURA, GANADERÍA Y PESCA. La FAO ratifica a CONABIA como Centro de Referencia en Bioseguridad. 25 de abril de 2019. Available at: https://www.argentina.gob.ar/noticias/la-fao-ratifica-conabia-como-centro-de-referencia-en-bioseguridad. Accessed on: 3 Set 2020.

NEW ZEALAND. Ministry for the environment. **Hazardous Substances and New Organisms Act 1996**. public act 1996, n. 30, section 1(2). Wellington, 2019. Available at: http://www.legislation.govt.nz/act/public/1996/0030/latest/DLM381222.html. Accessed on: 20 May 2020.

OSTP - OFFICE OF SCIENCE AND TECHNOLOGY POLICY. Coordinated framework for regulation of biotechnology products. **Fed Regist** 51:23,302–23,367. 26 June, 1986.

PARAGUAY. Resolución MAG No. 565, de 13 de mayo de 2019. Ministerio de Agricultura y Ganadería (MAG). Available at: https://www.inbio.org.py/wp-content/uploads/Resoluci%C3%B3n-565-de-2019.pdf. Accessed on: 17 May 2020.

RUFFELL, D. The EU Court of Justice extends the GMO Directive to gene-edited organisms. **FEBS Letter**, v. 592, n. 22, p. 3653-3657, 2018.

SATO, S**. Agricultural Biotechnology Annual:** Tokyo, 2019. USDA, 2020. Available at: https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=Agricultural%20Biotechnology%20Annual_Tokyo_Japan_10-20-2019. Accessed on: 2 Set 2020.

SCHULMAN, A. A.-O.; OKSMAN-CALDENTEY, K. M.; TEERI, T. H. European Court of Justice delivers no justice to Europe on genome-edited crops. **Plant Biotechnology Journal**, v. 18, n. 1, p. 8-10, 2020.

USDA Foreign Agricultural Service. Global Agricultural Information Network. GAIN Report: Argentina. Agricultural Biotechnology Annual. 15 de febrero de 2019. Available at: https://apps.fas.usda.gov/newgainapi/api/report/downloadreportbyfilename?filename=Agricultural%20Biotechnology%20Annual_Buenos%20Aires_Argentina_2-15-2019.pdf. Accessed on: 17 May 2020.

WHELAN, A. I.; LEMA, M. A. Regulation of genome editing in plant biotechnology: Argentina. In: Regulation of Genome Editing in Plant Biotechnology. Springer, Cham, 2019. p. 19-62.

WHELAN, A. I.; LEMA, M. A. Regulatory framework for gene editing and other new breeding techniques (NBTs) in Argentina. GM Crops & Food, v. 6, p. 253–265, 2015.

ZIMNY, T.; SOWA, S.; TYCZEWSKA, A.; TWARDOWSKI, T. Certain new plant breeding techniques and their marketability in the context of EU GMO legislation - recent developments. **New Biotechnology**, v. 51, p. 49-56, 2019.