Regulatory Constraints and Differences of Genome-Edited Crops Around the Globe

Penny Hundleby and Wendy Harwood

Abstract Plant breeding for centuries has relied on the availability of genetic variation to introduce new desirable traits into crops. Biotechnology has already accelerated the ability to induce and utilize new genetic variation, through approaches such as mutation breeding and using technologies such as marker assisted breeding to rapidly identify the required variation. These technologies fall within the definition of "conventional and traditional" breeding and are lightly regulated. However, plant breeders are facing an urgent need for access to wider genetic variation to meet the needs of today's farmers and consumers worldwide. New breeding technologies (NBTs), such as genome editing, are speeding up the breeding process and providing plant breeders with access to a far greater range of genetic variation. Coupled with a rapidly accelerating genomics era, genome editing is moving plant breeding into an exciting era of intelligent and precision-based plant breeding. The speed at which these new technologies are emerging has challenged the regulatory climate. Some countries consider genome edited crops to require the same regulatory oversight as genetically modified organisms (GMOs), while others have chosen to regulate with the same safety evaluations currently associated with bringing conventionally bred crops to market. Harmonization of the regulatory climate is urgently needed if there is to be equal access to this technology and to support international trade of these crops. The current chapter provides a global overview of the current regulatory status of genome-edited crops.

Keywords New breeding techniques · CRISPR · Gene editing · Genome editing · Regulation

P. Hundleby (✉) · W. Harwood
Department of Crop Genetics, John Innes Centre, Norwich, UK
e-mail: penny.hundleby@jic.ac.uk

S. H. Wani, G. Hensel (eds.), *Genome Editing*,
https://doi.org/10.1007/978-3-031-08072-2_17

1 Introduction

Plant breeders over the centuries have continued to exploit the availability of genetic variation, to meet human needs for increased yields, flavor, and nutritional and visual qualities, together with improved agronomic performance. While breeders initially sought genetic variation from landraces and heirloom varieties, the emergence of mutation breeding in the 1940s allowed for the artificial induction of new genetic variation (or mutations) into plant genomes. The approach is crude, introduces thousands of random mutations, but allows for desirable new traits to be identified and introduced into breeding programs. Although several rounds of backcrossing were also required to remove the unwanted mutations, the technology greatly increased the amount of genetic variation available to breeders. The first commercial varieties developed through mutation breeding were registered in the 1950s, and now over 3348 varieties are listed on the FAO/IAEA Mutant Variety Database (FAO/IAEA 2021).

Inevitably some of the new desirable traits introduced, such as higher yields, better flavor etc., have come at the expense or loss of others (e.g., loss of disease or insect resistance) with modern agriculture now heavily reliant on human inputs. Today, farmers across the globe are facing huge challenges. There are currently less farmers per capita than ever before, faced with producing more food for a growing population, on less land, in a changing climate. Pressures on governments to also recognize the need to protect the environment have resulted in the sudden removal of some agrochemicals and resources. This has resulted in the urgent need for increased availability to genetic variation, to find genetic solutions to address some of these challenges. With conventional plant breeding, taking some 10–15 years to get new crops to the market, genome editing not only offers access to precision breeding but also greatly reduces the time frames needed to generate new varieties.

Take, for example, the introduction of powdery mildew resistance in wheat. This story starts in barley, where natural and induced loss-of-function mutations of the *Mildew resistance locus o* (*Mlo*) gene were identified that confer broad-spectrum resistance against most *B. graminis* f. sp. hordei (*Bgh*) isolates. These mlo mutants have been providing mildew resistance in barley in the field for more than 40 years. BLASTING the *Mlo* genetic sequence against the wheat genome identified three orthologues of the barley *Mlo*, *TaMlo-A1*, *-B1*, and *-D1* (Konishi et al. 2010), on chromosomes 5AL, 4BL, and 4DL of wheat (Elliott et al. 2002). Genome editing techniques, such as TALENS and CRISPR, have successfully been applied to target and knock out all three copies of this gene to successfully introduce mildew resistance into wheat (Wang et al. 2014). Interestingly, the same end point could also be achieved in wheat using mutation breeding. Using a TILLING approach (Acevedo-Garcia et al. 2017), mutant lines have been identified and crossed together to combine all the required mutant knockouts needed to confer resistance to mildew. However, from a breeder perspective, the TILLING approach also brings in thousands of undesirable mutations that then need to be removed, taking much longer to achieve the same end point. So, while scientifically the gene editing approach offers

a faster and more precise approach for the introduction of mildew resistance into wheat, the TILLING approach currently faces less regulatory burden than gene editing.

While genome editing technologies have been around for some time, in the form of zinc finger nucleases (ZFNs), meganucleases, and transcription activator-like effector nucleases (TALENs) (Songstad et al. 2017), it was the publication of CRISPR/Cas9 (clustered regularly interspaced short palindromic repeats and *CRISPR*-associated protein 9) as a genome editing approach in plants, in 2013 (Feng et al. 2013; Zhang et al. 2017), that really made genome editing highly accessible to the scientific community. Since then, CRISPR/Cas9 as a simple genome editing tool for both research and commercial purposes has seen a continuous exponential rise, evidenced by the volume of publications, making it the most favored genome editing tool.

The sudden flood of activity and attention on genome editing also highlighted the need for clarity on how genome edited crops would be regulated. While some countries were quick to adapt their current legislations or release guidelines supporting the use of genome editing, others have not moved past seeing all organisms derived by genome editing as GMOs. This has led to confusion by plant breeders and the seed industry, with these unharmonized regulatory approaches likely to hinder technology applications and future trade between countries.

2 Paving the Way

Since 2015, several countries have outlined their regulatory path and clarified which types of genome-edited crops will not be regulated as GMOs. These include countries from North and South America together with Israel/Japan and Australia. These countries, perhaps unsurprisingly, are also strong supporters of GM technology, with all but Israel and Japan commercially growing GM crops. Argentina was the first country to proactively support the technology by providing clarity on the regulatory status in 2015; followed by Australia in 2016; Chile and Israel in 2017; Brazil, Columbia, and Paraguay in 2018/2019; and Japan in 2019. To best explain the regulatory approach, it is important to understand that not all genome editing is the same. Regardless of the different genome editing technologies used to create the edits, they all use site-directed nucleases (SDN), and three classes of genome editing exist:

1. Where a directed DNA double-strand break is repaired by the plants' own mechanism of non-homologous end joining without using an added repair template, often resulting in small mutations (SDN-1).
2. Where a template-guided repair is made, by an external DNA-template sequence that introduces one or several small mutations (SDN-2).
3. The insertion of a longer DNA sequence, including entire genes, through template-guided repair of the targeted double strand break (SDN 3) (Podevin et al. 2013).

In this chapter, we focus mainly on SDN1 and SDN2 as these technologies result in end products that are indistinguishable from those achieved via conventional biotechnology. As such, these are the products that have led some countries to view them in the same way as conventionally bred crops. For SDN-3 most, if not all jurisdictions, are in agreement and consider these products to not be exempt from their GMO regulations, and as such these crops will be assessed on a case-by-case basis. It is important to recognize that genome editing technologies cannot currently be used to achieve all the required changes needed to develop future improved crops and that a GM approach will still be needed in some cases.

With the regulatory climate currently differing across the globe, this will have serious implications on which countries will realistically have access to these technologies (i.e., will not be hampered by expensive and time-consuming additional regulatory burden) and the impact on trade that will inevitably be encountered. As previously seen with older GM technology, non-harmonious and asynchronous approvals delay commercialization and increase costs (Bullock et al. 2021).

3 The Need for Clarity

In October 2018, eight countries (Argentina, Australia, Brazil, Canada, Guatemala, Honduras, Paraguay, and the USA) came together to issue a joint statement to the World Trade Organization (USDA 2018) "supporting relaxed regulations for gene editing, stating that governments should 'avoid arbitrary and unjustifiable distinctions' between crops developed through gene editing and crops developed through conventional breeding. The ministries agreed to avoid obstacles, without a scientific basis, for the commercialization of products improved by genome editing, exchange information about products, developments and applicable regulations, and explore opportunities for regional harmonization." By November 2018, the number of countries adding support to the statement had risen to include Colombia, the Dominican Republic, Jordan, Uruguay, Vietnam, and the Secretariat of the Economic Community of West African States (USDA 2018). Over time more countries have come to a similar viewpoint, in considering simple genome editing, i.e., where no foreign genetic sequence is introduced, to be indistinguishable and equivalent to conventionally bred crops and therefore should be regulated in a similar way.

The impact of viewing gene editing as GM could have disastrous effects for crop improvement. Gene editing could allow companies to focus on output traits that may have a higher value to the consumer, as opposed to the input traits associated with GM technology that favor the producer. The costs associated with regulatory compliance of GM have restricted its use, mainly, to four high value commodity crops (soybean, maize, cotton, and oilseed rape) and input traits (herbicide tolerance and insect resistance), gene editing therefore shows great potential to move into a wider range of crops (Jorasch 2019). Yet the regulatory uncertainty is clearly having an impact, with companies already choosing not to develop products for countries where regulatory clarity is still sought. In the following section, we look at the

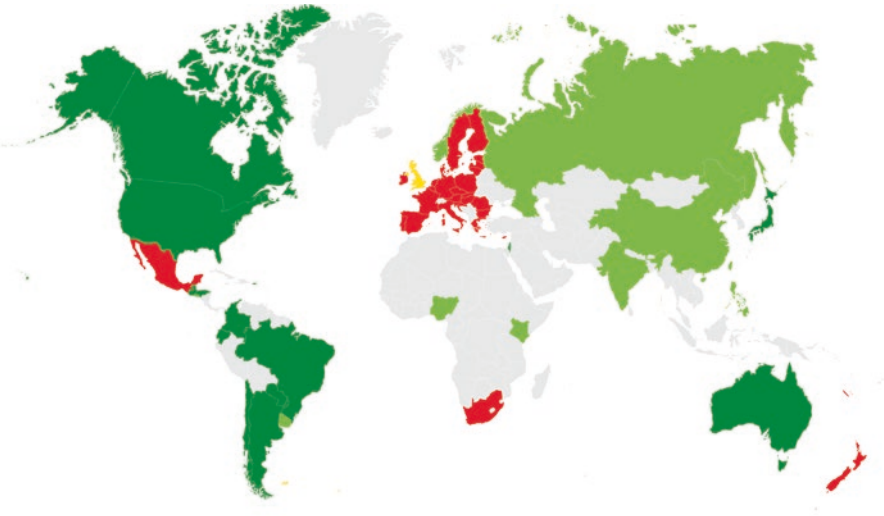

Fig. 1 Regulatory status of gene-edited crops (when no foreign DNA is inserted). Dark green = regulated as conventional crops. Pale green = draft regulations suggest they will be regulated as conventional crops. Red = viewed as GMOs. Yellow = under review but likely to be viewed favorably. The UK (shown in yellow) recently gave the go ahead for research field trials to proceed without the need for GMO regulatory oversight (when no foreign DNA is inserted); however, restrictions currently remain for commercial applications. Further amendments are still under review but look favorable

current regulatory climate for genome/gene editing across South, North, and Central America, across Europe, Africa, Russia, Asia, and the Southern Hemisphere. We also provide an "at a glance" global map summary of the regulatory status in Fig. 1.

4 The Regulatory Climate

4.1 South America

For countries in South America who have issued statements, no new legislation has been introduced, and gene-edited crops that do not contain DNA from another species are regulated as conventional plants. However, a dossier is required to be submitted to grant the exemption.

4.1.1 Argentina

Gene-edited crops are regulated as conventional plants unless they contain foreign DNA (Alfredo Lema 2019).

Argentina has always been a strong supporter of biotechnology (ranking third largest land area of cultivated biotech crops in 2019 (ISAAA 2019)) and has grown GM crops since cultivation first began in 1996. Having benefitted economically from the cultivation of these crops, it is perhaps unsurprising that Argentinian regulators where among the first to proactively issue clarity on the regulatory status of these still emerging technologies in 2015.

The Argentine regulatory system regulates gene-edited crops as conventional plants unless they contain foreign DNA. However, the regulatory system still requires developers to submit a dossier to the Argentine Biosafety Commission (CONABIA), who oversee GMOs, to determine this exemption. Gene-edited crops are assessed on a case-by-case basis by CONABIA, who are required to respond to submissions within 60 days as to whether the crop will be subject to GMO regulations. CONABIA considers (a) the techniques used in the process, (b) the genetic change in the final product, and (c) the absence of foreign DNA (transgenes) in the final product. Even if a crop is considered exempt from GMO regulations, if it has characteristics that present the probability of significant risk, the crop would undergo further monitoring by authorities and would be regulated as a GMO.

The Argentine authorities have engaged well with the public, organizing workshops and debates. The public's response suggests confidence in the regulatory oversight and welcomed that developers were local and focused on products suited to local markets and consumer and environmental benefits (Entine et al. 2021).

4.1.2 Uruguay

No unique regulations relating to GE have been issued.

In 2018, Uruguay joined the countries mentioned in Sect. 3 in signing the joint statement to the World Trade Organization supporting relaxed regulations for gene editing (USDA 2018), thus suggestive of supporting regulating gene-edited crops as conventional plants unless they contain foreign DNA. Plants containing foreign DNA would be regulated in line with GM regulations, as overseen by the National Biosafety Cabinet (GNBio), which oversees the Ministers of Agriculture, Economy, Environment, Health, Industry, and Foreign affairs. However, to date no specific regulations for gene-edited crops have been issued (Uruguay, Global Gene Editing Regulation Tracker 2020).

4.1.3 Paraguay

Gene-edited crops are regulated as conventional plants unless they contain foreign DNA (Benitez Candia et al. 2020).

Paraguay was the sixth largest producer of transgenic crops in 2019 (ISAAA 2019), and gene-edited crops can be expected to play a part in the countries' future agricultural landscape, although gene-edited crops have yet to be submitted for approved for commercial production in Paraguay. In 2018, Paraguay signed the

joint statement issued to the World Trade Organization supporting relaxed regulations for gene editing (Sect. 3), and in 2019, Paraguay published a resolution outlining the information required for crops developed using gene editing and other new breeding techniques (NBTs) to be approved. Gene-edited crops and food will be regulated as conventional plants unless they contain foreign DNA but will require the submission of a dossier to determine exemption. Gene-edited crops are assessed on a case-by-case basis by the National Commission on Agricultural and Forestry Biosafety, whereas genetically modified plants are regulated by the Ministry of Agriculture and the Biosecurity Commission (COMBIO).

4.1.4 Chile

Gene-edited crops are regulated as conventional plants unless they contain foreign DNA.

Chile has taken a similar view to other South American countries and considers gene-edited crops to be regulated as conventional plants unless they contain foreign DNA. However, they also require the submission of documents to the Ministry of Agriculture's Agricultural and Livestock Services (SAG) who will assess on a case-by-case basis gene-edited crops. In 2017, SAG published a statement on new breeding techniques (NBTs), stating that gene-edited crops that do not contain "a new combination of genetic material" are not subjected to GMO regulations (Sanchez 2020).

4.1.5 Brazil

Gene-edited crops are regulated as conventional plants unless they contain foreign DNA.

Brazil, with the second largest land area of cultivated GM crops in 2019 (ISAAA 2019), has also taken the position that gene-edited crops and food should be regulated as conventional plants unless they contain foreign DNA. In Brazil, GMOs are governed by the National Technical Commission for Biosafety (CTNBio). In 2018, CTNBio released Normative Resolution No. 16, focusing on NBTs. It clarified that many products derived from NBTs do not meet the definition of a GMO, as defined by the 2005 regulation, and concluded that NBTs should be regulated on a case-by case basis. This resolution establishes the requirements for whether a product can be exempt from the GMO regulatory framework.

Regulations focus on the characteristics of the final product rather than the process used to create it. CTNBio will assess the risk level of each newly developed plant or food, whether new (foreign) genetic material has been introduced and whether the product has already been approved for commercialization in other countries. CTNBio will then respond to the applicant within 20–90 business days. Applications have already been submitted to CTNBio for gene-edited tomatoes, soybeans, and a "waxy" maize with extra starch, while four gene-edited varieties of

yeast for production of bioethanol and other purposes were approved by CTNBio in 2018 (Brazil: Global Gene Editing Tracker 2020). As of September 2020, there had been 23 consultations with CTNBio, for products not considered to fall within the scope of the GMO law 11.105/2005. This clarity has resulted in several new startup companies and strengthening of medium to large national companies working on NBTs (Entine et al. 2021).

4.1.6 Ecuador

Gene-edited crops are regulated as conventional plants unless they contain foreign DNA.

In Ecuador, the Ministry of Agriculture and Livestock regulates GM crops through the National Agrarian Authority (Norero 2017), and while the country has not embraced GM technology, and currently prohibits the commercial cultivation of genetically modified crops, the situation looks more favorable for gene-edited crops. For gene-edited crops that do not contain DNA from another species, these will be regulated in the same way as conventionally bred plants, while GE crops that contain foreign DNA will be viewed as GM. The regulation is based on the Organic Code of the Environment, issued in 2019, that established exemptions from the very restrictive GMO regulations (Entine et al. 2021).

4.1.7 Colombia

Gene-edited crops are regulated as conventional plants unless they contain foreign DNA but require notification to the authorities to approve the exemption.

Columbia also signed the 2018 joint statement to the WTO, in support of relaxed regulations for gene editing, and in the same year the Colombian Agricultural Institute (ICA) issued a resolution that established a case-by-case consultation process to determine if a gene-edited product would be considered a GMO (Gatica-Arias 2020). Once notified, the ICA must respond to applicants within 60 days as to whether the organism will be subject to GMO regulations. For a gene-edited crop not to be considered GMO, it must not contain genes from another species that have been introduced through modern biotechnology techniques.

4.2 Central America

4.2.1 Honduras, Guatemala, and El Salvador

Gene-edited crops that do not contain foreign DNA are not regulated as GMOs.

In 2018, Honduras and Guatemala signed the joint statement to the WTO supporting a more relaxed regulatory oversight for plant gene editing, while in 2019,

Honduras, Guatemala, and El Salvador also signed an inter-ministerial agreement to harmonize the research and commercialization of crops developed through biotechnology. This agreement required each country to create a national advisory committee for the risk assessment and evaluation of GMOs for agricultural use. The agreement also defines the term "novel combination of new genetic material," setting the legal basis to define gene-edited products (which do not fulfil the definition of GMOs) as conventional. In 2019, Honduras published a resolution to establish a streamlined authorization procedure for crops developed using new breeding techniques (NBTs) and in doing so became the first country in Central America to regulate products of NBTs. Overseen by the National Service of Food Safety Plant and Animal Health (SENASA), Honduras follows in line with the Cartagena Policy on Biosafety and considers that technologies, which result in an organism equivalent and indistinguishable from products of conventional (traditional) plant breeding, should be regulated in the same way to allow producers and consumers to gain from these technologies (Macall 2020). El Salvador is expected to follow Honduras' lead. Of the three countries, only Honduras is currently growing GM crops (GM maize on less than 0.1 Mha) (ISAAA 2019).

While Guatemala does not currently grow GM crops, they have looked at the implications the regulations may have on imports and have clarified that imports of GE seed/plants will not be regulated as GM if they do not contain foreign DNA.

4.3 North America

4.3.1 Mexico

Gene-edited crops are currently regulated under laws established for transgenic GMOs.

Mexico is yet to determine the regulatory status of gene editing crops, and products are currently regulated under laws established for transgenic GMOs (Mexico: Global Gene Editing Regulator Tracker 2020). The Secretariat of Health (SALUD) is responsible for regulating GM crops, and currently Mexico only grows a modest amount of GM cotton. This regulatory oversight puts Mexico at a very different standpoint to other countries in the American continent.

4.3.2 USA

Gene-edited crops that do not contain foreign DNA are not regulated as GMOs.

The USA is the largest grower of biotech crops in the world (ISAAA 2019) and was the first country to approve a genome-edited product for commercial sale. This was a soybean product with no trans-fats and lower saturated fat produced by the Minnesota-based company Calyxt (2019) using a technique called TALENs.

The enthusiastic uptake of gene editing technology in the USA is perhaps supported by the fact that even the introduction of GM technology back in the 1990s did not trigger the need for new regulations as such but instead relied on existing regulatory frameworks to oversee these new crops. Up to three different agencies are involved in the process, depending on the final product and how the plant was produced (USDA 2021a):

1. The US Department of Agriculture's Animal and Plant Health Inspection Service (USDA – APHIS) is responsible for protecting agriculture from pest and diseases. Crops considered to pose an agricultural "risk" are deemed "regulated articles" and are reviewed to ensure that, under the proposed conditions of use, they do not present a plant pest risk by ensuring appropriate biosafety systems are in place to minimize such risks, such as handling, confinement, and disposal of crops. There is also a petition process where applicants can make a case for a GM product to be considered for "non-regulated status" if an applicant can provide enough evidence that the product does not pose a risk to agriculture. This is then added to a federal register where the public can submit comments for consideration on the environmental assessment before the petition is granted, i.e., given with a "non-regulated" status.
2. The Environmental Protection Agency (EPA) regulates pesticides and therefore regulates biotech crops that have pesticide properties (e.g., insect-resistant crops).
3. The Food and Drug Administration (FDA) oversees food safety.

In 2015, President Obama issued an Executive Order "Memorandum on Modernizing the Regulatory System for Biotechnology Products" directing the USDA, EPA, and FDA to update regulatory roles and responsibilities under the Coordinated Framework for the Regulation of Biotechnology, to develop a long-term strategy to ensure that the regulatory system was future proof for new biotech products. The "National Strategy for Modernising the Regulatory System for Biotechnology Products" and "Update to the Coordinated Framework for regulation of Biotechnology" were released by the White House Office for Science and Technology Policy (OSTP 2016, 2017).

In 2019, President Trump signed an executive order directing federal agencies to streamline the regulatory process for biotech crops by exempting low-risk products from the existing rules and creating a unified platform that outlines the regulatory requirements from all three agencies, for the review and authorization of products developed using biotechnology. In 2020, USDA-APHIS finalized what it called the SECURE (sustainable, ecological, consistent, uniform, responsible, efficient) rule, which would exempt (i.e., not regulate) gene-edited plants that otherwise could have been developed through conventional breeding. This reaffirms a focus on regulating characteristics of gene-edited plants, instead of the process used to create them, as is the case in the EU, for example. APHIS states that these exemptions are intended to bring the regulation of potential GE plants more in line with the guidelines for conventionally bred crops. Therefore, gene-edited crops that do not contain foreign DNA are not regulated as GMOs, if they pose no risk to other plants, and show no food safety attributes different to those of traditionally bred crops. In these

cases, the crops will not be subject to pre-market regulatory evaluation; however, it will be the responsibility of the developer to assure that products placed on the market are safe for use and consumption (as in the case for conventional crops).

The FDA (which oversees food safety) and EPA (which regulates pesticides) have not announced if their existing policies and regulations related to GMOs would be used to regulate gene-edited crops and food.

4.3.3 Canada

Only gene-edited crops with novel traits will be regulated as PNTs (Friedrichs et al. 2019).

Canada has a well-established product-orientated approach to policy and regulatory oversight and regulates all plants with novel traits (PNTs), regardless of the technology used to create them.

Although Canada appears to be headed toward regulating gene-edited crops lightly (having also signed the joint statement to the WHO), there remains uncertainty as to what types of gene editing will trigger oversight, i.e., what is considered "novel" and what that level of oversight might be. Currently, GMOs on the market in Canada pass through Health Canada and the Canadian Food Inspection Agency (CFIA) where new organisms are categorized as either "novel" or "non-novel." The context of gene editing is as follows.

"Novel" organisms have traits that are not naturally occurring and have not previously been approved for sale by Health Canada and the CFIA. Organisms that pose an obvious risk, such as those containing potential allergens or those that contain foreign DNA in the final product, are considered novel. Such crops will require *pre-market safety assessment*s, and the associated costs incurred could potentially be prohibitive, limiting certain lower value crops from being developed.

"Non-novel" organisms are organisms that have a history of safe use, show no characteristics that are new to the species, and do not contain genetic material from another organism after its genome has been edited. For these crops no pre-market safety assessments are required.

Most crop varieties produced via chemical or radiation-based mutagenesis are not considered to have novel traits and therefore are not subject to pre-market assessment and are regulated as conventional crops. While most of the early gene-edited crops are viewed as products of a more precise version of mutagenesis, there remains some uncertainty as to whether the regulators will view them as such, as no formal framework or decisions have yet been issued. However, a herbicide-tolerant oilseed rape developed using the NBT technique known as ODM (oligonucleotide-directed mutagenesis) was approved in 2013 (Halford 2019).

A consultation exercise "Proposed new guidelines for Novel Food Regulations" focused on plant breeding was recently carried out in Canada (Health Canada, 2021) which should hopefully lead to more clarity. Better defining what is considered novelty is critical. Currently PNT regulations could apply to any new crop with a trait that expresses 25–30% higher or lower than the conventional variety (Entine

et al. 2021). Thus, it will be the novelty of the crop, and not how it was made, that will trigger regulatory oversight. This will have implications for trade, if the same products are viewed by other countries as not requiring regulatory oversight.

4.4 Europe

4.4.1 The European Union (EU)

Gene-edited crops are regulated as GMOs.

The European Union represents 27 member state (MS) countries and currently regulates all genome-edited crops as GMOs under the 2001/18 EU GMO Directive. The Directive defines a GMO as "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" but excludes several traditional breeding technologies that fit this description, listing them in Annex 1B of the directive. Among the techniques listed for exclusion from the directive is mutagenesis. Prior to 2018, several MS had interpreted the exemption to also include genome-edited crops that had been edited in ways that would result in a product indistinguishable to one obtained through traditional mutagenesis techniques (i.e., chemical or radiation-induced mutagenesis). In 2016, nine NGOs filed a case to the French Courts, which was later referred to the Court of Justice of the European Union (CJEU), to challenge the status quo as they viewed the exclusion on genome editing to be allowing "GM through the backdoor." In July 2018, the CJEU confirmed that organisms obtained by newer methods of direct mutagenesis such as genome editing were not excluded from the scope of the EU GMO directive (CJEU 2018). Overnight CRISPR field trials went from being "unregulated" to regulated.

The CJEU ruling of 2018 was met with frustration by researchers and plant breeding companies, with over 117 research facilities signing a position paper urging the European Policy Makers to act to safeguard Europe's competitiveness on these new technologies (MPG 2019). For many the ruling fell short of delivering clarity on the regulatory status of gene editing and how such crops would be monitored (Van der Meer et al. 2021).

The European Commission Chief Scientific Advisors criticized the EU court ruling, and the EU Council later requested that the EU Commission conduct a study regarding the CJEU judgment. The results of this consultation study were published in April 2021 and concluded that the current GMO legislation was not fit for purpose for some NGTs and their products and that it needed to be adapted to scientific and technological progress (European Commission 2021). The lack of clarity surrounding the future regulatory climate for gene-edited crops has resulted in several EU-based companies focusing on the development of GE crops for non-EU markets (Jorasch 2019).

During this period, in 2020, France's top administrative court also ruled that the French High Council for Biotechnology (HCB) needed to set up a specific list of mutagenesis techniques, or methods, that will be exempted from GMO restrictions

(technologies that fulfil the requirement of "having been conventionally used in a number of applications and have a long safe history of use"). Depending on the list, France could even regulate plants that have been developed by earlier mutagenesis techniques, e.g., herbicide-tolerant crops, if the HCB concludes that the abovementioned requirement is not met. This would have huge implications for France, as one of the EU's largest agricultural producers, as it would effectively deny French farmers access to much of the common seed catalogue.

4.4.2 The UK

Gene-edited crops are currently regulated as GMOs in line with the EU, but this position is currently under review following UK's departure from the EU.

The UK formally left the European Union on January 23, 2020. This gave the UK scope, should they wish, to deviate from the restrictive GMO EU Directive and set their own regulatory path. Within the UK, England, Scotland, Northern Ireland, and Wales have national laws that control the deliberate release of GMOs into the environment. In England, the Department of Environment, Food and Rural Affairs (Defra) is the competent national authority responsible for the environmental release of GM plants. All applications submitted to Defra are passed on to the statutory Advisory Committee on Releases to the Environment (ACRE) that was appointed under section 124 of the UK Environmental Protection Act 1990 (EPA) to provide advice to government regarding the release and marketing of GMOs. The committee works within the legislative framework set out by "Part VI of the EPA" and, within England, the GMO Deliberate Release Regulations 2002 Act, which together implement EU Directive 2001/18/EC. The principal role of ACRE is to consider each application on a case-by-case basis and evaluate the risks to human health and the environment.

In early 2021, Defra launched a consultation exercise to gain feedback from various stakeholders on their views regarding gene editing; this consultation closed on March 17, 2021. The results of the consultation exercise, and an announcement by the UK Government on Genetic Technologies, were published on the September 29, 2021. In this they set out their plans for a two-step reform. The first step removes the regulatory burden for research groups by enabling the field trials of gene-edited crops (free from transgenes) to go ahead without being subject to existing GMO rules. Researchers will still be required to notify Defra. The second step will be to "bring forward primary legislation at a suitable opportunity to amend the regulatory definitions of a GMO to exclude organisms that have genetic changes that could have been achieved through traditional breeding or which could occur naturally" (Defra 2021). These crops would then be regulated in line with conventional crops and "novel food" oversight (FSA 2020) where appropriate. This could allow for much easier trade relationships with counties who have adopted a similar regulatory view. The 'New Genetic Technologies (Precision Breeding) Bill' was brought to Parliament in 2022, and is likely to conclude early 2023. However, the impact on trade with the EU is perhaps one of the biggest hurdles to overcome, if the UK regulates differently to the EU.

While the UK government has generally been supportive of the potential of GM technology, commercial cultivation of GM crops has never taken place in the UK. The only approved GM crop for cultivation in the EU currently is the insect-resistant maize (MON810), for which there is no demand by British farmers. Field testing of GMOs and gene-edited crops are currently permitted in the UK, and field trials of CRISPR gene-edited plants were conducted in line with Part B of the 2001/EU GMO directive (Faure and Napier 2018; Neequaye et al. 2021), until April 2022 when the rules changed to permit field trials of gene edited crops (where no foreign DNA is present) to proceed under a simple on-line notification system to Defra, and no longer requiring a GMO licence.

4.4.3 Norway

It has been proposed that gene-edited crops that do not contain DNA from another species be regulated as conventional plants but would still require notification.

Biotechnology in Norway is regulated by the Ministry of Agriculture, the Ministry of Environment, and the Ministry of Health. The Directorate for Nature Management is responsible for feed and seed, and Norwegian Food Safety Authority is responsible for biotech food. Genetically modified food is regulated by the Matloven Food Act and the Gene Technology Act, one of the world's strictest, which requires that genetically modified products contribute to sustainable development in order to be approved (Norway: Global Gene Editing Regulation Tracker 2020). In fact, Norway has a long history of opposition to transgenic crop biotechnology, generally opposing the cultivation of GMOs and being more restrictive than the EU regarding imports. *Although Norway is part of the European Economic Area, it is not a full European Union Member, as such it is not bound by EU Directives but generally implements EU Directives.*

In 2018, the Norwegian Biotechnology Advisory Board proposed a tiered regulatory system in which genetic changes that can arise naturally or can be achieved using conventional breeding methods would be regulated as conventional plants. However, they would still require that a notification is submitted to the government, while crops developed using cisgenics (introduction of genes from within species) would require expedited but limited assessment and approval. Genetic changes that cross species barriers (transgenics) or involve synthetic DNA sequences would still require assessment and approval under strict GMO regulations. Although these regulations appear to pave the way for the introduction of gene-edited crops, Norway's historical, public, and political opposition to crop biotechnology remains among the most intense in Europe; it will be interesting to see if these relaxed guidelines support innovation in this sector or merely act to support the import of such crops.

4.5 Israel

Gene-edited crops that do not contain DNA from another species are regulated as conventional plants.

As is the case in several of the countries reviewed in this chapter, Israel has also chosen to regulate gene-edited crops and food in line with conventional plants, unless they contain foreign DNA. Gene-edited crops will be assessed on a case-by-case basis based on the characteristics of the final product and will require a dossier to be submitted to determine if they are exempt. There are no commercially available genetically modified or gene-edited plants cultivated in Israel, although GM crops are currently imported.

Genetically modified organisms are regulated by the Ministry of Agriculture and Rural Development and the Ministry of Health. The Ministry of Agriculture and Rural Development oversees the Plant Protection and Inspection Service (PPIS) and the Israeli National Committee for Transgenic Plants (NCTP). In 2016, the NCTP concluded that gene-edited crops that do not contain DNA from other species would not be subject to GMO regulations, as regulated by the Seed Regulation Act of 2005.

The Ministry of Health stated that all new food products, including conventional crops and gene-edited ones, must undergo risk assessment before approval. Israel's Ministry of Agriculture announced in 2019 plans to invest in establishing a National Genome Editing Centre (Menz et al. 2020).

4.6 Africa

The regulatory status of gene-edited crops has not yet been determined, but draft guidelines have been approved in Nigeria.

Africa is a region where gene editing holds great promise in addressing a wide range of issues, including malnutrition and crop failure linked to climate change. Yet, in general, Africa has lagged behind other nations in setting out and developing their biosafety laws, although in recent years there has been much progress. The number of countries growing GM crops commercially rose to six in 2019 and included Nigeria (who also became the first country to approve Bt cowpea), Ethiopia and Malawi, together with countries with a longer history of growing GM such as South Africa, Sudan, and Eswatini. There has also been progress in biotech research, regulation, and acceptance in Mozambique, Niger, Ghana, Rwanda, Zambia, and Kenya. Burkina Faso and Egypt have grown GM crops in the past. As African countries are still, in many cases, defining their biosafety laws, this may be an advantage when it comes to assessing how to regulate gene editing. Nigeria, South Africa, Kenya, and Eswatini are currently taking the lead in amending their regulations to accommodate gene editing (Komen et al. 2020). Nigeria became the first African country to publish their draft guidelines "National biosafety guidelines for the regulation of gene editing" (USDA 2021b). This followed an amendment to the National Biosafety Management Agency (NBMA) Act of 2019, section 25(A) that states "No person, institute or body shall carry out gene drive, gene editing and synthetic biology except with the approval of the Agency." While Kenya has yet to publish its guidelines, the country has approved six GE projects for contained use research (Obi 2021).

South Africa, which has led on the commercial cultivation of transgenic crops in Africa, is yet to clarify its position and publish guidelines for the cultivation of GE crops.

4.7 Russia

Decree suggests that gene editing techniques will not be prohibited in the same way as GMOs.

Russia is a vast land area spanning both Europe and Asia and has historically been rather opposed to genetic modification, with no commercial cultivation of GM crops, although allowing imports. Plants developed through biotechnology are currently regulated by three separate organizations: the Federal Service for Surveillance of Consumer Rights Protection and Human Welfare (Rospotrebnadzor) being responsible for developing legislation on genetically modified food products and monitoring the effect on human and the environment health; the Ministry of Agriculture which develops policy for the use of genetically modified crops and organisms in agriculture; and the Federal Service for Veterinary and Phytosanitary Surveillance (VPSS) which is responsible for overseeing genetically modified crops for feed.

The countries' view on gene editing appears to be more supportive, with a large investment in R&D of the technology. A 111-billion-rouble (US$1.7Bn) federal research program sets out to develop 10 new varieties of gene-edited crops and animals by 2020 and another set of 20 gene-edited varieties by 2027 (Dobrovidova 2019). The decree establishing the program describes gene editing as equivalent to conventional breeding methods, the view adopted by most of the world. The decree lists four crops – barley, sugar beet, wheat, and potatoes – as priorities for development. The program, which was announced in April 2019, also attracted interest because it suggests that some gene-edited products will now be exempt from a law passed in 2016 that prohibits the cultivation of genetically modified (GM) organisms in Russia, except for research purposes. Previously, it was unclear whether gene-edited organisms were included in the ban.

4.8 Asia

4.8.1 China

Gene editing regulations for plants have not yet been announced, but they are expected to be regulated as conventionally bred plants.

With a population of 1.4 billion people, China has the largest population in the world. It was ranked seventh in the world for global area of transgenic crops in 2019 (ISAAA 2019) mainly growing GM cotton and papaya, and its recent approval of

GM corn and soybean is set to increase its biotech area further, thus reducing its reliance on imports from other GM nations.

While China currently limits the import and cultivation of genetically modified crops, it is thought that China will follow other countries in regulating most gene editing techniques as conventional plants. The Ministry of Agriculture regulates genetically modified crops in China, subjecting them to the 2001 Regulations on Administration of Agricultural Genetically Modified Organisms Safety.

China is yet to announce the regulatory status of gene-edited crops, but the government has invested heavily in agricultural research projects over the past decade, and China has published more research papers on CRISPR than any other country.

In 2017, state-owned ChemChina bought Switzerland-based Syngenta, one of the world's four largest agribusinesses and a company deeply involved in gene-editing research, for $43 billion. This sizable investment could suggest a positive future for biotech crops in China.

4.8.2 Japan

Gene-edited crops must be registered but do not require safety or environmental testing unless foreign DNA is present.

Japan became the first country to approve a gene-edited tomato for the home growers' market in 2021, making this the world's first approved direct consumption product. Produced by the Japanese-based company Sanatech Seed, the tomato contains higher levels of GABA, a compound reported to lower blood pressure and relieve stress (Sanatech Seed 2020). This shows Japan's support for this new technology, which contrasts with its view on GM technology, for which there has never been approval for commercial cultivation, although GM imports are allowed. Gene-edited crops are assessed on a case-by-case basis and do require submission of notification to the government, which includes providing information on the editing technique and genes targeted for editing. Safety and environmental assessments are required only when the plant contains foreign DNA. However, each time a gene-edited crop is crossed with another conventional or gene-edited crop, a separate notification process must occur. Local governments may also set additional regulatory requirements for gene-edited crops (USDA 2020).

Four ministries currently regulate genetically modified plants: the Ministry of Agriculture, Forestry and Fisheries (MAFF), the Ministry of Health, Labour and Welfare (MHLW), the Ministry of Environment (MOE), and the Ministry of Education, Culture, Sports, Science and Technology (MEXT). The Food Safety Commission (FSC), an independent risk assessment body under the Cabinet Office, performs food and feed safety risk assessment for MHLW and MAFF.

4.8.3 India

Draft guidelines suggest that SDN-1 gene editing will be lightly regulated, while the rest will require additional tests and approvals.

In 2020, the Department of Biotechnology published a draft document for the regulatory framework and guidelines for risk assessment of genome-edited organisms (Ministry of Science and Technology, Government of India 2020). In the proposal a tiered regulatory approval process is suggested. Group I would cover products of SDN-1 and would require confirmation and notification of the gene edit. Group II would cover SDN-2 techniques and would require more intensive field trials and data to ensure the edits were successful, and Group III – plants with large DNA changes, including insertion of foreign DNA (SDN-3 techniques) – would require the same extensive testing and regulatory oversight as GMOs, including field trials to test safety to human health, animals, and the environment.

4.9 Southern Hemisphere

4.9.1 New Zealand

All gene-edited crops are currently regulated as GMOs.

In 2014, the New Zealand Environmental Protection Authority (EPA) – who oversees GMOs under the Hazardous Substances and New Organisms (HSNO) Act of 1996 – initially ruled that plants produced via gene editing methods, where no foreign DNA remained in the edited plant, would not be regulated as GMOs. However, following a challenge in the High Court, this decision was overturned such that New Zealand currently regulates all products of gene editing as GMOs, even if they do not incorporate any foreign genes. New Zealand has yet to update its policy and, so far, appears to be waiting to see how its major trading partners (Europe, Asia, and Australia) conclude on their approach to regulating these crops.

In 2018, the Environment Minister, together with support from researchers, called for an update to the HSNO Act, stating that the current position did not support innovation and made it practically impossible to obtain approval for gene-edited crops, with no clear pathway to market. Currently no gene-edited plants are commercially grown in New Zealand, and no applications for a full environmental release have been received by the EPA (Fritsche et al. 2018).

4.9.2 Australia

SDN-1 gene editing organisms are regulated as conventional plants, while the rest are regulated as GMOs, requiring pre-market approval.

Australia was also a signatory to the 2018 joint statement to the World Trade Organization supporting relaxed regulations for gene editing, and on the April 10, 2019, the Australian government announced it would not regulate gene editing

techniques in plants, animals, and human cell lines that do not introduce new genetic material (Mallapaty 2019). In an amendment to the Gene Technology Regulations (GTR) of 2001, clarifications on NBTs that are not considered GMOs were defined (OGTR 2019). The amendments mean SDN-1 gene-edited organisms are not considered to be GMOs provided that (a) no nucleic acid template was added to the cells to guide genome repair following site-directed nuclease application and (b) the organism has no other traits from gene technology (e.g., a cas9 transgene, or an expressed SDN protein) in the final product.

It becomes the responsibility of the developer to ensure products comply with the law and that these requirements have been met. Some methods used to generate SDN-1 organisms produce GMOs as an intermediate step, and in these cases while transgenes are still present the plants will continue to require authorization under the *Gene Technology Act of 2000.* This approach is in agreement with many other countries considered above.

When a crop no longer falls within the regulatory oversight of the GTR, it is overseen by the Department of Agriculture, Water and the Environment, and should it produce food products, such products are regulated under the Australia New Zealand Food Standards Code. No gene-edited crops have yet been put forward for approval yet in Australia.

In addition to the EPA in New Zealand and the GTR in Australia, the joint Food Standards Australia New Zealand (FSANZ) authority sets food standards, including regulations regarding gene edited food, which are compiled in the Australian and New Zealand Food Standard Code. The Food Standards Code requires pre-market approval and adherence to labeling standards for food produced using any gene technology, including any imported food that was produced through gene technology.

FSANZ recently reviewed how food developed using NBTs will be regulated (as GMOs or not), and in December 2019, FSANZ released a report that made three recommendations: (1) "to revise and modernise the definitions in the Code to make them better able to accommodate existing and emerging genetic technologies; (2) to consider process and non-process-based definitions and the need to ensure that NBT foods are regulated in a manner that is commensurate with the risk they pose; (3) to ensure there is open communication and active engagement with all interested parties and to explore ways to raise awareness about GM and NBT foods" (FSANZ 2019).

A proposal to amend the definitions in the Code commenced in February 2020; however, due to the COVID-19 pandemic, FSANZ postponed the release of the first call for submissions for public consultation and has yet to make any changes to the Food Standard Code as a result. As such the current pre-market approval and labeling requirements will continue to apply.

5 Conclusion

As a society, we are increasingly becoming aware of the challenges facing farmers, producers, and policy makers, on how to feed a growing population, in a way that both protects and nurtures the environment. Climate change is happening now, and

we need to find ways to produce new crops that can mitigate climate change, reduce the need for chemical inputs, and meet the needs of society. There are many ways that we will achieve these goals, and indeed it will take a holistic approach to meet the ambitious targets that have been set, such as EU's Farm to Fork Policy targets for 2030 and European Green Deal for 2050 (EC 2021). Similar targets are being set in other jurisdictions. In breeding timescales, if we consider the generation times needed to breed new varieties, those dates are not that far away.

Genome editing is one technology that is uniquely placed to help speed up the breeding process, taking advantage of the innovations in precision breeding and the availability of vastly increased genomic knowledge.

In some cases, gene editing reaches the same end point as conventional breeding but gets there with a greater degree of precision and speed, enabling breeders to address urgent goals with greater confidence. When multiple gene targets are involved, it moves plant breeding into a new realm of possibilities. It could also enable more nutritious and diverse foodstuffs (regulations permitting) and the domestication of new crops, further expanding agricultures biodiversity and a move away from large monocultures.

The science is advancing rapidly, with the future of gene editing allowing for targeted and stacked gene insertions, chromosome engineering, epigenetic edits, and more. However, the regulatory climate is often slower to catch up. Already for simple SDN-1 gene editing, our review shows that the consensus on how to regulate such crops is not yet harmonized at the global level. Countries that are slow to clarify their position on gene editing risk being left behind and farmers losing out on competitive technologies. Furthermore, such disharmony will create barriers to trade, with gene-edited crops requiring different regulatory requirements in different countries. This could make countries who consider all gene-edited crops as GMOs less desirable trading partners. Regardless of the regulatory challenges ahead, continually advancing genome editing technologies are such a valuable addition to the tools currently available to breeders that we can look forward to their increased adoption, delivering vital new genetic variation for crop improvement.

Acknowledgments We acknowledge and thank Lucy Anderson, a student from the University of East Anglia for producing the map in Fig. 1, while on her student placement working with Ruby O'Grady from the communications team at the John Innes Centre. We acknowledge funding support from the Biotechnology and Biological Sciences Research Council (BBSRC) Institute Strategic Programmes GRO [BB/J004588/1] and GEN [BB/P013511/1] to the John Innes Centre.

References

Acevedo-Garcia J, Spencer D, Thieron H, Reinstaedler A, Hammond-Kosack K, Phillips AL, Panstruga R (2017) mlo-based powdery mildew resistance in hexaploid bread wheat generated by a non-transgenic TILLING approach. Plant Biotechnol J 15:367–378

Alfredo Lema M (2019) Regulatory aspects of gene editing in Argentina. Transgenic Res 28:147–150

Benitez Candia N, Fernandez Rios D, Vicien C (2020) Paraguay's path toward the simplification of procedures in the approval of GE crops. Front Bioeng Biotechnol 8
Brazil (2020) Crops/Food. Globabl Gene Editing Tracker (2020). Accessed June 2021 at Brazil: Crops/Food | Global Gene Editing Regulation Tracker (geneticliteracyproject.org)
Bullock DW, Wilson WW, Neadeau J (2021) Gene editing versus genetic modification in the research and development of new crop traits: an economic comparison JEL codes. Am J Agric Econ
Calyxt (2019) Press release February 26, 2019 available at 'First commercial sale of Calyxt high oleic soybean oil on the U.S. Market » Calyxt'. Accessed June 2021
CJEU (2018) Court of Justice of the European Union. Press release No. 111/18. July 25th 2018. Accessed at 'Organisms obtained by mutagenesis are GMOs and are, in principle, subject to the obligations laid down by the GMO Directive (europa.eu)', June 2021
Defra (2021) Genetic technologies regulation – GOV.UK (www.gov.uk). Accessed 29 Sept 2021
Dobrovidova O (2019) Russia joins global gene-editing bonanza. Nature 569:319–320
EC (2021) European Commision sustainability targets: accessed at Farm to Fork Strategy (europa.eu) and the A European Green Deal | European Commission (europa.eu), June 2021
Elliott C, Zhou FS, Spielmeyer W, Panstruga R, Schulze-Lefert P (2002) Functional conservation of wheat and rice Mlo orthologs in defense modulation to the powdery mildew fungus. Mol Plant-Microbe Interact 15:1069–1077
Entine J, Felipe MSS, Groenewald J-H, Kershen DL, Lema M, McHughen A, Nepomuceno AL, Ohsawa R, Ordonio RL, Parrott WA, Quemada H, Ramage C, Slamet-Loedin I, Smyth SJ, Wray-Cahen D (2021) Regulatory approaches for genome edited agricultural plants in select countries and jurisdictions around the world. Transgenic Res
European Commsion (2021) Food safety. EC study on new genomic techniques (europa.eu). Accessed June 2021
FAO/IAEA Mutant Viriety Database (2021) Available online at https://mvd.iaea.org. Accessed June 2021
Faure JD, Napier JA (2018) Europe's first and last field trial of gene-edited plants? elife 7:e42379. Published 2018 Dec 18. https://doi.org/10.7554/eLife.42379
Feng Z, Zhang B, Ding W, Liu X, Yang D-L, Wei P, Cao F, Zhu S, Zhang F, Mao Y, Zhu J-K (2013) Efficient genome editing in plants using a CRISPR/Cas system. Cell Res 23:1229–1232
Friedrichs S, Takasu Y, Kearns P, Dagallier B, Oshima R, Schofield J, Moreddu C (2019) An overview of regulatory approaches to genome editing in agriculture. Biotechnol Res Innov 3(2):208–220. https://doi.org/10.1016/j.biori.2019.07.001
Fritsche S, Poovaiah C, MacRae E, Thorlby G (2018) A New Zealand perspective on the application and regulation of gene editing. Front Plant Sci 9:1323. https://doi.org/10.3389/fpls.2018.01323
FSA (2020) Food Standards Agency. Novel foods authorisation guidance. Accessed at Novel foods authorisation guidance | Food Standards Agency on June 2021
FSANZ (2019) Food Standards Australia New Zealand. Final report: review of food derived using new breeding techniques. Accessed at NBT Final report.pdf (foodstandards.gov.au), June 2021
Gatica-Arias A (2020) The regulatory current status of plant breeding technologies in some Latin American and the Caribbean countries. Plant Cell Tissue Organ Cult 141:229–242
Halford NG (2019) Legislation governing genetically modified and genome-edited crops in Europe: the need for change. J Sci Food Agric 99:8–12
ISAAA (2019) International Service for the Acquisition of Agri-biotech Applications. Accessed June 2021. www.isaaa.org
Jorasch P (2019) The global need for plant breeding innovation. Transgenic Res 28:81–86
Komen J, Tripathi L, Mkoko B, Ofosu DO, Oloka H, Wangari D (2020) Biosafety regulatory reviews and leeway to operate: case studies from sub-Sahara Africa. Front Plant Sci 11:130
Konishi S, Sasakuma T, Sasanuma T (2010) Identification of novel Mlo family members in wheat and their genetic characterization. Genes Genet Syst 85:167–175
Macall D (2020) Honduras opens the door to genome editing technologies in agriculture. Published 27th June 2020. Accessed at Honduras opens the door to genome editing technologies in agriculture (diegomacall.com), June 2021

Mallapaty, S. (2019) Australian gene-editing rules adopt 'middle ground'. Nature
Menz J, Modrzejewski D, Hartung F, Wilhelm R, Sprink T (2020) Genome edited crops touch the market: a view on the global development and regulatory environment. Front Plant Sci 11:1525. https://doi.org/10.3389/fpls.2020.586027
Mexico (2020) Crops/Food. Globabl Gene Editing Tracker (2020). Accessed June 2021 at Mexico: Crops / Food | Global Gene Editing Regulation Tracker (geneticliteracyproject.org)
Ministry of Science and Technology (2020) Department of Biotechnology, Government of India. F=Draft document on genome edited organisms: regulatory framework and guidelines for risk assessment. Accessed at Draft_Regulatory_Framework_Genome_Editing_9jan2020a.pdf (dbtindia.gov.in) on June 2021
MPG (2019) Max-Planck-Gesellschaft. Press release July 29th 2019. 'Scientists call for modernization of EU gene-editing legislation | Max-Planck-Gesellschaft (mpg.de)'. Accessed June 2021
Neequaye M, Stavnstrup S, Harwood W, Lawrenson T, Hundleby P, Irwin J, Troncoso-Rey P, Saha S, Traka MH, Mithen R, Østergaard L. CRISPR-Cas9-Mediated Gene Editing of MYB28 Genes Impair Glucoraphanin Accumulation of Brassica oleracea in the Field. CRISPR J. 2021 Jun;4(3):416-426. doi: 10.1089/crispr.2021.0007. PMID: 34152214
Norero D (2017) Ecuador passes law allowing GMO crop research. Genetic Literacy Project, published June 20th, 2017. Accessed June 2021
Norway (2020) Crops/Food | Global Gene Editing Regulation Tracker (2020) (geneticliteracyproject.org). Accessed June 2021 at Norway: Crops/Food | Global Gene Editing Regulation Tracker (geneticliteracyproject.org)
Obi, L. (2021) Kenya approves 6 gee-edited crops as it pursues food security, sustainable farming. Genetic literacy project: Business Daily Africa. Published 4th February 2021. Accessed at Kenya approves 6 gene-edited crops as it pursues food security, sustainable farming | Genetic Literacy Project, June 2021
OGTR (2019) Office of the Gene Technology Regulator. 2019 amendments to the regulations. Accessed at OGTR | 2019 Amendments to the Regulations on June 2021
OSTP (2016) Office of Science and Technology Policy. National strategy for modernizing the regulatory system for biotechnology products. Accessed at biotech_national_strategy_final.pdf (archives.gov), June 2021
OSTP (2017) Office of Science and Technology Policy. Update to the coordinated framework for the regulation of biotechnology. Accessed at '2017_coordinated_framework_update.pdf (archives.gov)', June 2021
Podevin N, Davies HV, Hartung F, Nogue F, Casacuberta JM (2013) Site-directed nucleases: a paradigm shift in predictable, knowledge-based plant breeding. Trends Biotechnol 31:375–383
Sanatech Seed (2020) Press release 11.12.20. Launch of the genome-edited tomato with increased GABA in Japan | サナテックシード株式会社 (sanatech-seed.com)
Sanchez MA (2020) Chile as a key enabler country for global plant breeding, agricultural innovation, and biotechnology. GM Crop Foods 11(3):130–139
Songstad DD, Petolino JF, Voytas DF, Reichert NA (2017) Genome editing of plants. Crit Rev Plant Sci 36:1–23
Uruguay (2020) Crops / Food | Global Gene Editing Regulation Tracker (2020) (geneticliteracyproject.org). Accessed June 2021 at https://crispr-gene-editing-regs-tracker.geneticliteracyproject.org/uruguay-crops-food/#
USDA (2018) WTO members support policy approaches to enable innovation in agriculture. Press release 0239.18. URL: https://www.usda.gov/media/press-releases/2018/11/02/wto-members-support-policy-approaches-enable-innovation-agriculture. Accessed 10 June 2021
USDA (2020). Agricultural biotechnology annual. Country Japan. Report No. JA2019-0219 Published March 30, 2020. Accessed at DownloadReportByFileName (usda.gov), June 2021
USDA (2021a) Regulation of biotech plants. Accessed June 2021 at Regulation of Biotech Plants | USDA

USDA (2021b) Government of Nigeria approved National Biosafety Guideline on Gene Editing. Accessed at DownloadReportByFileName (usda.gov), June 2021

Van der Meer P, Angenon G, Bergmans H, Buhk H, Callebaut S, Chamon M et al (2021) The status under EU law of organisms developed through novel genomic techniques. Eur J Risk Regul 1–20. https://doi.org/10.1017/err.2020.105

Wang Y, Cheng X, Shan Q, Zhang Y, Liu J, Gao C, Qiu J-L (2014) Simultaneous editing of three homoeoalleles in hexaploid bread wheat confers heritable resistance to powdery mildew. Nat Biotechnol 32:947–951

Zhang H, Zhang J, Lang Z, Botella JR, Zhu J-K (2017) Genome editing-principles and applications for functional genomics research and crop improvement. Crit Rev Plant Sci 36:291–309