RESOURCE DOCUMENT

# Gene Editing for Sustainable Agriculture and Food Security in Asia-Pacific Region

Asia-Pacific Association of Agricultural Research Institutions
APAARI

Asia-Pacific Consortium on
APCoAB
Agricultural Biotechnology

BCIL

한국바이오안전성정보센터
KOREA BIOSAFETY CLEARING HOUSE

KI PA BiC
한국아시아바이오안전협력진흥원
KOREA INSTITUTE FOR PROMOTING ASIA BIOSAFETY COOPERATION

2023

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**Disclaimer:** This Resource Document has been prepared based on webinars and published resources. The contents do not reflect views of organisations supporting this initiative or members of steering committee constituted to guide the process of conducting webinars

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# FOREWORD

The advent and importance of agricultural biotechnology to meet the challenges of food security has been well documented for producing crops with improved agronomic traits and enhances resilience to biotic and abiotic stresses. The transgenic crops brought with it a plethora of risk assessment protocols and biosafety regulations. Over the past few years the continuous innovation in plant breeding techniques have shown the possibilities to produce plants that would not conform with the definition of a Living Modified Organism (LMO) in the Cartagena Protocol on Biosafety, or with the classical definition of Genetically Modified Organisms (GMOs) in other standard setting bodies. Such is the case with gene edited plants, and many countries are reviewing their GMO regulations to address possible inconsistencies and clarify regulatory pathways. Keeping this in view the Asia-Pacific Association of Agricultural Research Institutions (APAARI) has initiated discussions on the development of gene edited products and the emerging policies that may govern their introduction into the market. In collaboration with other international agencies, and with the guidance of a Steering Committee of international experts, APAARI hosted webinars that fostered awareness of gene editing and emerging policies in different parts of the world, and has developed this Resource Document "Gene Editing for Sustainable Agriculture and Food Security in Asia-Pacific Region" with the support of experts.

This Resource Document is an outcome of the deliberations of the webinars and published literature. The document in its five chapters highlights the potential contribution of gene editing in enhancing food security and provides an overview of the of the science behind genome editing, providing details on different methods to effect alterations in the genome. Most importantly it gives existing and emerging policies for genome edited plants in different countries. It brings out the fact that there is a growing consensus that gene edited plants that do not contain exogenous DNA will not be regulated as transgenics or as classical GMOs. Many countries have already decided to regulate SDN-1/SDN-2 genome edited products in the same way as products of conventional breeding. Also listing of bodies which may play a crucial role in harmonizing regulations and facilitating trade of agricultural trade of gene edited products is dealt with.

Keeping in view the fact that Asia-Pacific countries include a wide diversity of economies and different levels of scientific expertise and regulations, attempts have been made to provide science-informed Policy recommendations to maximize the potential of gene editing for sustainable agriculture and food security in the region. It is hoped that the document would serve as a scientific base for those countries which are in the state of developing or may develop policies in gene editing. This would eventually help in harmonization of the guidelines and policies in the region and thus facilitate more research, innovation and trade.

I am grateful to esteemed Steering Committee members for providing guidance for conduct of webinars that served as foundation for preparation of the Resource Document. Thanks to Dr. Norwati Adnan, Malaysia, Dr. Flerida Carino, Philippines, Dr. Ho-Min Jang, Korea, Dr. Ryo Ohsawa and Dr. Manabu Takahara from Japan, Dr. Morven A McLean, USA, Dr. Heidi Mitchell, Australia, Dr Roland Schafleitner and Professor Chwan-Yang HONG from Taiwan and Late Dr. Kiran K. Sharma, India.

I am thankful to Dr. Rishi Tyagi, Former Co-ordinator, APCoAB and Dr. Vibha Ahuja, Chief General Manager, BCIL, Co-conveners of the Steering Committee, for compiling the document with support from Dr. Sasireka Rajendran, Technical Coordintor, APAARI and Dr. Arlene Asthana Ali, Senior Project Executive, BCIL. I also thank Dr. Flerida Carino and Dr. Jimmy Botella for their contribution in providing expert inputs during the process of preparation of the document.

I also acknowledge the funding support to APCoAB from Ministry of Agriculture, Taiwan & Australian Centre for International Agricultural Research (ACIAR) and for resource documents from Korea Biosafety Clearing House (KBCH) and Korea Institute for Promoting Asia Biosafety Cooperation (KIPABIC)

**Ravi Khetarpal, Ph.D**
Executive Director, APAARI

# ACRONYMS AND ABBREVIATIONS

| | |
|---|---|
| **APAARI** | Asia-Pacific Association of Agricultural Research Institutions |
| **APCoAB** | Asia-Pacific Consortium on Agricultural Biotechnology and Bioresources |
| **BARC** | Bangladesh Agricultural Research Council |
| **BAS** | Bangladesh Academy of Sciences |
| **BEs** | Base editors |
| **BCIL** | Biotech Consortium India Limited |
| **BIOTEC** | National Center for Genetic Engineering and Biotechnology |
| **CAC** | Codex Alimentarius Commission |
| **CBD** | Convention on Biological Diversity |
| **CFIA** | Canadian Food Inspection Agency |
| **CJEU** | European Court of Justice |
| **CPB** | Cartagena Protocol on Biosafety |
| **CRISPR** | Clustered Regularly Interspaced Short Palindromic Repeats |
| **DBT** | Department of Biotechnology |
| **DNA** | Deoxyribonucleic acid |
| **DSBs** | Double-strand breaks |
| **DUS** | Distinctness, uniformity, stability |
| **EC** | European Commission |
| **EPA** | Environmental Protection Agency |
| **EU-SAGE** | European Sustainable Agriculture through Genome Editing |
| **FAO** | Food and Agriculture Organization of the United Nations |
| **FIFRA** | Federal Insecticide, Fungicide, and Rodenticide Act |
| **FFDCA** | Federal Food, Drug, and Cosmetic Act |
| **FSANZ** | Food Standards Agency of Australia New Zealand |
| **GABA** | Gamma-Aminobutyric Acid |
| **GE** | Genetically engineered |
| **GMAC** | Genetic Modification Advisory Committee |
| **GMOs** | Genetically Modified Organisms |
| **gRNA** | guide RNA |
| **IPPC** | International Plant Protection Convention |
| **ISTA** | International Seed Testing Association |
| **KBCH** | Korea Biosafety Clearing House |
| **LMO** | Living Modified Organism |
| **MAGyP** | Ministry of Agriculture, Livestock and Fisheries of Argentina |
| **MARA** | Ministry of Agriculture and Rural Affairs |

| | |
|---|---|
| **MoEF&CC** | Ministry of Environment, Forest and Climate Change |
| **MHESI** | Ministry of Higher Education, Science, Research and Innovation |
| **MHLW** | Ministry of Health, Labour & Welfare |
| **MOTIE** | Ministry of Trade, Industry and Energy |
| **NBC** | National Biosafety Committee |
| **NBMA** | National Biosafety Management Agency |
| **NBTs** | New breeding techniques |
| **NCBP** | National Committee on Biosafety of the Philippines |
| **NCTP** | National Committee for Transgenic Plants |
| **NIBGE** | National Institute for Biotechnology and Genetic Engineering |
| **NIH** | National Institutes of Health |
| **NGTs** | New genomic techniques |
| **ODM** | Oligonucleotide Directed Mutagenesis |
| **OECD** | Organization for Economic Co-operation and Development |
| **OGTR** | Office of Gene Technology Regulator |
| **PBI** | Plant breeding innovations |
| **PIPs** | Plant-incorporated protectants |
| **PNTs** | Plants with novel traits |
| **RNPs** | Ribonucleoproteins |
| **SDG** | Sustainable Development Goals |
| **SDN** | Site Directed Nucleases |
| **SECURE** | Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient Rule |
| **SFA** | Singapore Food Agency |
| **SMEs** | Small- and medium-sized enterprises |
| **SPS** | Sanitary and phytosanitary |
| **SOPs** | Standard Operating Procedures |
| **SSNs** | Sequence-Specific Nucleases |
| **TALEN** | Transcription activator-like effector nucleases |
| **USDA-APHIS** | United States Department of Agriculture-Animal and Plant Health Inspection Service |
| **VAAS** | Vietnam Academy of Agricultural Sciences |
| **WHO** | World Health Organization |
| **WTO** | World Trade Organization |
| **ZFNs** | Zinc finger nucleases |

# SUMMARY

In 2015, the United Nations adopted “The 2030 Agenda for Sustainable Development”, providing for “a shared blueprint for peace and prosperity for people and the planet, now and into the future”. The Agenda articulated the 17 Sustainable Development Goals (SDG), an urgent call for global; partnership among all countries, regardless of level of development. The first three development goals seek to end poverty and hunger, and to improve health and well-being of all people. Plant agricultural biotechnology has the potential for making significant contributions towards attaining these goals. The challenge is to make various stakeholders recognize this potential and find opportunities in the plant biotechnology sector.

Ensuring food security can significantly alleviate poverty and hunger, and enhance global well-being of all populations. The pillars of food security includes food availability, food accessibility, food utilization, stability, agency and sustainability. Agricultural biotechnology offers opportunities for each of these pillars by reducing losses due to wastage and biotic and abiotic factors, by increasing yield, and improving the nutritional quality of crops.

Agricultural biotechnology has utilized recombinant DNA technology to produce several crops with improved agronomic properties, and enhanced resilience to pests, diseases and adverse environmental conditions (e.g., drought and flooding). The technology has also been used to improve the nutritional quality of crops and reduce anti-nutritive food components inherently present or produced during processing. More recently, the agricultural biotechnology toolbox has been expanded by the addition of newer molecular plant breeding techniques (NBTs) that make targeted changes within the plant DNA to alter specific traits, the toolkit commonly referred to as genome (or gene) editing. The toolbox is still expanding and techniques being used for gene editing include mega nucleases, ZFNs, TALEN, CRISPR systems, Oligonucleotide Directed Mutagenesis (ODM), base editing, prime editing etc.

Anticipating the eventual introduction of gene edited plants and their products in the market, the Asia-Pacific Association of Agricultural Research Institutions (APAARI) has initiated discussions on the development of gene edited products and the emerging policies that may govern their introduction into the market. In collaboration with other international agencies, and with the guidance of a Steering Committee of international experts (Annexure-1), APAARI hosted webinars that fostered awareness of gene editing and emerging policies in different parts of the world, and has called for harmonization of policies at least within the region.

This Resource Document on “Gene Editing for Sustainable Agriculture and Food Security in Asia-Pacific Region” is an outcome of the deliberations of the webinars and published literature. The document has five chapters.

Chapter 1 highlights the potential contribution of gene editing in enhancing food security and provides an overview of the science behind the techniques. The Chapter also gives a summary of gene editing research and development activities of different countries. It emphasizes the need for crafting new policies for products of gene editing and calls for harmonization of these policies to minimize disruption in food trade and ensure wide acceptability of foods derived from gene-edited plants.

Chapter 2 gives an overview of the science behind genome editing, providing details on different methods to effect alterations in the genome. It also presents more details on the status of gene edited plants under development and provides a rich source of reference materials and links to databases to facilitate a more comprehensive understanding of this technique.

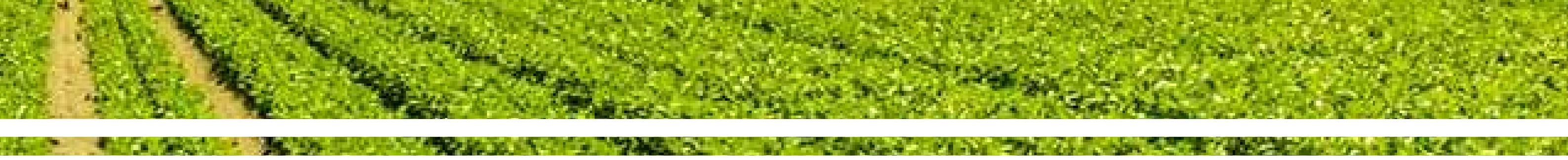
Existing and emerging policies for genome edited plants are provided by Chapter 3. In most of the countries surveyed, there is a growing consensus that gene edited plants that do not contain exogenous DNA will not be regulated as transgenics or as classical genetically modified organisms (GMOs). Many countries are inclined to regulating SDN-1/SDN-2 genome edited products in the same way as products of conventional breeding.

Chapter 4 lists international standard setting bodies that contribute to quality management of agriculture processes by developing standards and other measures. These bodies may play a crucial role in harmonizing regulations and facilitating trade of agricultural trade of gene edited products. The continuous innovation in plant breeding techniques may produce plants that would not conform with the definition of an LMO in the Cartagena Protocol on Biosafety, or with the classical definition of GMOs in other standard setting bodies. Such is the case with gene edited plants, and many countries are reviewing their GMO regulations to address possible inconsistencies and clarify regulatory pathways. Chapter 4 also emphasizes the need for harmonized, risk proportionate, compatible regulatory approaches to products of genome editing.

Policy recommendations have been provided in Chapter 5 to maximize the potential of gene editing for sustainable agriculture and food security in Asia-Pacific region. These recommendations are a result of the APAARI initiatives in holding consultations with various stakeholders under its Programme on the Asia-Pacific Consortium on Agricultural Biotechnology and Bioresources (APCoAB), in association with Korea Biosafety Clearing House (KBCH) and Biotech Consortium India Limited (BCIL).

The policy recommendations call for an enabling policy for innovations, science-informed, risk proportionate regulations, clarification of ambiguities and sharing of information. At the same time, building institutional capacity, human resource and public-private partnerships are key to ensure the expediting application of these advanced tools and technologies in the region. Regional collaborations and networks can contribute to capacity building, communication strategies, policy development and risk-benefit communication.

A High Level Policy Dialogue of the countries in the region would be very useful for assessing the status of institutional and regulatory capacities and the way forward specially for the developing the least developed countries.



## CHAPTER 1

# INTRODUCTION

## 1.1 Sustainable agriculture, food security and biotechnology

The Sustainable Development Goals were adopted in 2015 by all member states of the United Nations "to end poverty, protect the planet and improve the lives and prospects of everyone, everywhere." With 2030 as target achievement date, the top three goals relate to poverty eradication, improved food security, and promotion of health and well-being. The Food and Agriculture Organization of the United Nations (FAO) has defined "Sustainable Development" as the management of economic, social, and environmental resources and technological and institutional changes to attain and continue to meet the human needs of present and future generations[1]. In spite of notable progress in global hunger and poverty reduction over the last few decades, large population in developing countries are still not able to satisfy their basic needs. Close to eight hundred million people are undernourished and do not have sufficient access to calories, most of them living in Asia and Africa. The number has significantly grown since the outbreak of the COVID-19 pandemic. In 2021, more than 425 million people were affected by hunger in Asia and the situation is likely to become more challenging in coming years[2].

In agriculture, the greatest challenge is to feed the growing population and mitigate the negative impact of climate change. Sustainable intensification of agriculture is essential for accomplishing food and nutritional security and addressing the alarming concerns of climate change. Conventional breeding techniques have led to the development of many superior agronomically important traits in numerous crops. The adoption of modern biotechnology approaches further advanced and refined trait development and introduction which is not possible through conventional breeding. The potential of biotechnology in improving agricultural productivity, including that of smallholder farming systems, is also well recognized[3].

## 1.2 Genome editing in agriculture

Genome editing, also referred to as gene editing is one of the latest developments in molecular genetics and crop improvement technologies. Because this technology is more precise and efficient as compared to conventional breeding, gene editing can reduce the time needed to produce a new variety or breed and as such can lower research and development costs. Considered as a transformative innovation, significant applications have been reported since its discovery and its potential for plant breeding is extensively acknowledged.[4]

Targeted and controlled mutagenesis is increasingly being used by plant breeders, in both public and private sectors. The most used technologies in genome editing are CRISPR-Cas system (CRISPR stands for clustered regularly interspaced short palindromic repeats), transcription activator-like effector nucleases (TALENs), zinc finger nucleases (ZFNs), and homing endonucleases or meganucleases. The technologies used for genome editing work like molecular scissors, cutting the DNA in a specific location, then removing, adding, or replacing known DNA sequences where the cut was made. The reagents that specifically recognize and precisely cleave DNA targets within the genomes of living cells are referred to as site-directed nucleases (SDNs); also called sequence specific nucleases or SSNs. The primary task of the reagent is to find the specific DNA sequence target within a complex genome and make a targeted DNA

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[1] FAO (2021) The State of Food and Agriculture 2021. Making agri-food systems more resilient to shocks and stresses. Rome: FAO. doi:10.4060/cb4476en

[2] FAO (2022) The State of Food Security and Nutrition in the World 2022: Repurposing food and agricultural policies to make healthy diets more affordable. Rome, FAO. https://doi.org/10.4060/cc0639en

[3] FAO (2004) The State of Food and Agriculture 2003-2004. Agricultural Biotechnology: Meeting the Needs of
Poor? Food and Agricultural Organisation of United Nations, Rome. 208 p.

[4] Doudna J.A. and E. Charpentier. Genome editing (2014) The new frontier of genome engineering with CRISPR-Cas9. Science ; 346(6213):1258096.

double strand break. The cell then recognizes the broken chromosomes and activates one of the two primary DNA repair mechanisms. Depending on the type of DNA repair outcomes, three classes have been designated viz. SDN-1, SDN-2 and SDN-3[5,6]. SDN-1 produces a double-stranded DNA break that is repaired via nonhomologous end joining, a native intracellular repair mechanism which can result in the random addition or deletion of nucleotides, often causing a frameshift mutation. In SDN-2, the double-stranded break is repaired by homologous recombination, a different native intracellular repair mechanism which uses a DNA template to add, delete or replace specific nucleotides. Under natural conditions, the paired chromosome is the source of template DNA, but for use in genome editing, a synthetic DNA template that contains the desired sequence alteration is provided. By contrast, SDN-3 uses the same homologous recombination mechanism, but introduces a much larger gene segment, or whole gene(s) at a specific site in the genome using homologous recombination. This could result in a transgenic plant depending on the nature and origin of the introduced segment[7].

The explosion of interest in gene editing as expressed by the boom in scientific publications reflects the extraordinary flexibility and power of this new technology. Building on the increasing availability of pangenomes[8] and whole-genome DNA sequences for many crops, genome-editing technologies offer a relatively higher level of accuracy and predictability than technologies that produce genetically modified organisms (GMOs). The discovery of CRISPR/Cas9 has opened new avenues in genome editing. In general, applications of genome editing are potentially beneficial for nutritional enhancement, improvement of food safety and reduction of food waste for consumers, and resistance to diseases, pests and weeds. Genome editing may make seeds more affordable because of cheaper seed production. Genome editing may lead to development of plant varieties with enhanced climate resilience (e.g., drought tolerance), and ecosystem services.

Gene editing is already moving beyond the laboratory and is being applied to more than 65 crops across 55 countries, mostly addressing agronomy, food and feed quality, or abiotic stress tolerance[9,10]. Several genome-edited crops viz. soybean, canola, rice, maize, camelina, and teff have been or are in the process of commercialization[11]. It is interesting to note that genome edited crops under development are more diverse in terms of varieties and traits as compared to first generation GM crops. Further, more public organizations and smaller companies are engaged in research and development activities utilizing this technology for crop improvement.

One of the main advantages of using genome editing in crop improvement is that it can accelerate the delivery of improved varieties to smallholder farmers. Genes can be edited directly in elite breeding lines or commercial varieties, eliminating the need for backcrossing used in conventional plant breeding for introgression of a specific trait(s). This reduces the time needed to develop an improved variety by nearly two-thirds and eliminates linkage drag caused by non-elite residual genes from the donor parent. Several efforts in crop gene editing have been undertaken to improve performance across a range of crops and traits: climate resilience, heat or cold tolerance, rain-resistance, disease resistance, weed resistance, nutritional enhancement, and reduced allergenicity. Efforts to increase yield using gene editing

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[5] Lusser M, C. Parisi, E. Rodriguez Cerezo and D. Plan (2011) New plant breeding techniques. State-of-the-art and prospects for commercial development. EUR 24760 EN. Luxembourg (Luxembourg): Publications Office of the European Union; JRC63971

[6] Organisation for Economic Co-operation and Development (OECD) (2014) Consensus Documents for the Work on Harmonisation of Regulatory Oversight in Biotechnology: Facilitating Harmonisation. Report of the OECD workshop on environmental risk assessment (ERA) of products derived from novel plant breeding techniques (NPBT), 10 February 2014. ENV/JM/BIO(2015)5, https://one.oecd.org/document/ENV/JM/BIO(2015)5/en/pdf. Accessed on July 27, 2023

[7] Podevin N., H.V. Davies, F. Hartung, F. Nogue, and J.M. Casacuberta (2013) Site-directed nucleases: a paradigm shift in predictable, knowledge-based plant breeding. Trends in Biotechnology 31: 375–383

[8] Bayer P.E. A.A. Golicz, A. Scheben, J. Batley and D. Edwards (2020) Plant pan-genomes are the new reference. Nature Plants 6: 914–920

[9] Menz J., D. Modrzeweski, F. Hartung, R. Wilhelm and T. Sprink (2020) Genome Edited Crops Touch the Market: A View on the Global Development and Regulatory Environment. Frontiers of Plant Science 11, 586027

[10] Database of genome-edited crop plants by European Sustainable Agriculture Through Genome Editing (EU-SAGE). https://eu-sage.eu/genome-search Accessed on July 25, 2023

[11] Pixley K.V., J.B. Falck-Zepeda, R. L. Paarlberg, P.W.B. Phillips, I.H. Slamet-Loedin, K.S. Dhugga, H. Campos and N. Gutterson (2022) Genome-edited crops for improved food security of smallholder farmers. Nature Genetics 54: 364-367

have significant potential for reducing food insecurity, as well as combating effects of changing climates[12,13,14]. In addition, with genome editing, the natural ability of plants and soils to capture carbon from the atmosphere and store it for long periods of time can also be enhanced. Increasing plant biomass not only helps make agriculture more efficient, it reduces the need for chemical fertilizers and captures more carbon from the atmosphere.

Genome editing is at the initial stages and its more creative and precise applications in agriculture will appear with greater promises in future. Applications of gene-editing to advance agricultural sustainability and nutrition security are receiving significant interest, with a rich pipeline of gene edited plants being developed by public and private sector organizations across the Asian continent.

## 1.3 Emerging policies

In parallel to advancements in research and applications, discussions were held on whether gene edited plants should be treated in the same way as conventional breeding lines, or treated as GMOs. Most countries have undertaken a practical approach towards regulations particularly in cases where changes could have been made using conventional breeding. For genome edited products that lead to insertions of novel genes, the existing regulations for GM crops are being applied. Argentina was the first country to have enacted new regulations for products of new breeding techniques, which included genome editing. Subsequently, several countries viz. USA, Japan, Australia, Philippines, Nigeria, Brazil, India etc. have issued notifications/statements/amendments in their regulatory frameworks to clarify regulatory requirements for various categories of genome edited crops. The European Commision has recently proposed to exempt gene-edited plants from the current GMO law if the genetic change can occur naturally, or if such change may be brought about by conventional breeding subject to an appropriate verification procedure. There are countries, wherein discussions are still underway to decide on suitable path for genome edited products Developing countries particularly in Asia and Africa are also in the process of preparing their policy frameworks. Details are discussed in Chapter 3 of this publication.

## 1.4 Initiatives by APAARI

In anticipation of the eventual introduction of gene edited plants and their products in the world market, important regional consultations have been convened on gene editing in agriculture in Asia. *The 2nd Asia Forum on Genome Editing* was convened by Korea Biosafety Clearing House (KBCH) in Gangneung, Korea in November 2018[15]. The need for a regional cooperation system that could improve the level of safety management and follow-up on the world trends with regard to genome editing was deliberated. The Asia-Pacific Association of Agricultural Research Institutions (APAARI) and the International Crops Research Institute for the Semi-Arid Tropics (ICRISAT) convened the *Regional Expert Consultation on Gene Editing and its Regulation*[16] in Patancheru, India in October 2019 with an objective to highlight the innovations through gene editing, their potential impact in the agricultural sector and need for enabling policies. Harmonization of approaches within the Asia-Pacific region was highlighted for facilitating collaboration in research, capacity development, regulation, and trade.

In continuation to the above and in recognition of the need for objective, evidence-based information to support advancement of these recommendations, APAARI conceived the development of a comprehensive resource document. Such a document will provide governments and other interested stakeholders with information needed to inform policy development,

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[12] Karavolias N.G. (2021) Application of gene editing for climate change in agriculture. Frontiers in Sustainable Food System 5:685801

[13] Smyth S.J. (2022) Contributions of genome editing technologies towards improved nutrition, environmental sustainability and poverty reduction. Frontiers in Genome Editing 4: 2

[14] Mbaya H. S. Lillico, S. Kemp, G. Simm and A. Raybould (2022) Regulatory frameworks can facilitate or hinder the potential for genome editing to contribute to sustainable agricultural development. Frontiers in Bioengineering and Biotechnology 10

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[16] Tyagi R.K., R.K. Varshney, P. Bhatnagar-Mathur, S. Bajaj, R. Kumria and R.K. Khetarpal (2019) Regional Expert Consultation on Gene Editing and its Regulation - Proceedings and Recommendations. Asia-Pacific Association for Agricultural Research Institutions (APAARI), Bangkok, Thailand, xvii+44 p.

particularly as regards issues related to any potential regulation of gene edited plants.

As a first step towards the preparation of resource document, a series of webinars were organized to solicit inputs from global experts and key stakeholder groups on the important topics. In addition, the webinar series was also aimed towards spreading awareness among various stakeholders about gene editing techniques, recent advancements in the Asia-Pacific region, differential status of regulations and intellectual property rights landscape with respect to gene editing applications. A Steering Committee was set up to guide the process of conducting webinars, so that their inputs could be used for preparation of resource document (list of members at Annexure-1).

Members of the Steering Committee and other eminent experts led the discussions in the webinar series on “Applications of gene editing in sustainable agriculture and food security in Asia-Pacific region” organized in 2021. The three webinars’ topics were:

*i. Genome editing tools and its applications for targeted plant breeding*
*ii. Advancing genome edited plants from lab to land*
*iii. Enabling policies for genome editing in agriculture*

The webinars evinced great interest from various stakeholders not only from the Asia-Pacific region, but also from other countries. More than 2500 participants from 60 countries registered and on an average about 700 participated in each of the webinar.

Based on the learnings from webinar series and developments globally, this “Resource Document on Applications of Gene Editing in Sustainable Agriculture and Food Security in Asia-Pacific Region” provides an update on basics of genome editing, applications, regulatory approaches and trade-related aspects for gene editing in agriculture. The need for harmonized policies for facilitating availability of the crops in the Asia-Pacific Region for contributing to challenges viz food security and climate change, etc. are also deliberated in the document.

# CHAPTER 2
# PRIMER ON GENE EDITING

## 2.1 Mutagenesis for crop improvement

Genetic diversity lies at the heart of crop improvement, and for thousands of years this meant reliance on naturally occurring mutations followed by deliberate selection of varieties with favourable phenotypic traits. This process is unpredictable as it depends entirely on the random chance occurrence of beneficial spontaneous mutations along with chances of undesirable traits.

Early in the 20th century, plant breeders began using chemical mutagens or ionizing radiation (e.g., gamma rays or X-rays) to introduce large numbers of mutations within the plant genome, thus increasing the genetic variation available for further selection. Mutation breeding, i.e. the use of induced mutations in crop improvement, was first coined by Freisleben and Lein in 1944.[17] The first artificial random mutagenesis experiments in wheat, maize and barley were published in 1930[18]. Since then, commercial plant varieties obtained by artificial mutagenesis have grown to 3,402 in 2023, with the vast majority (2087) produced and commercialized in Asia (https://mvd.iaea.org/). The most common commercial crop obtained by random mutagenesis in Asia is rice, with the first variety produced in China and registered in 1957. The three most recently mutagenized varieties were produced in Bangladesh and India, and were registered in 2022. Aside from rice, commercial varieties generated by random mutagenesis in Asia include, wheat, soybean, barley, maize, millet, tomato, pigeon pea, rapeseed, mungbean, watermelon, chickpea, cucumber, pear, peach, orange, groundnut and Chinese cabbage[19].

Among the various plant breeding methods, mutation breeding has the greatest threat of unintended effects (Figure 1). Key drawbacks of this method include the non-specific nature of the generated mutations, the large amount of nucleotides simultaneously mutated, and common occurrence of deletions, duplications, or rearrangements of large genomic fragments.[20] The iden-

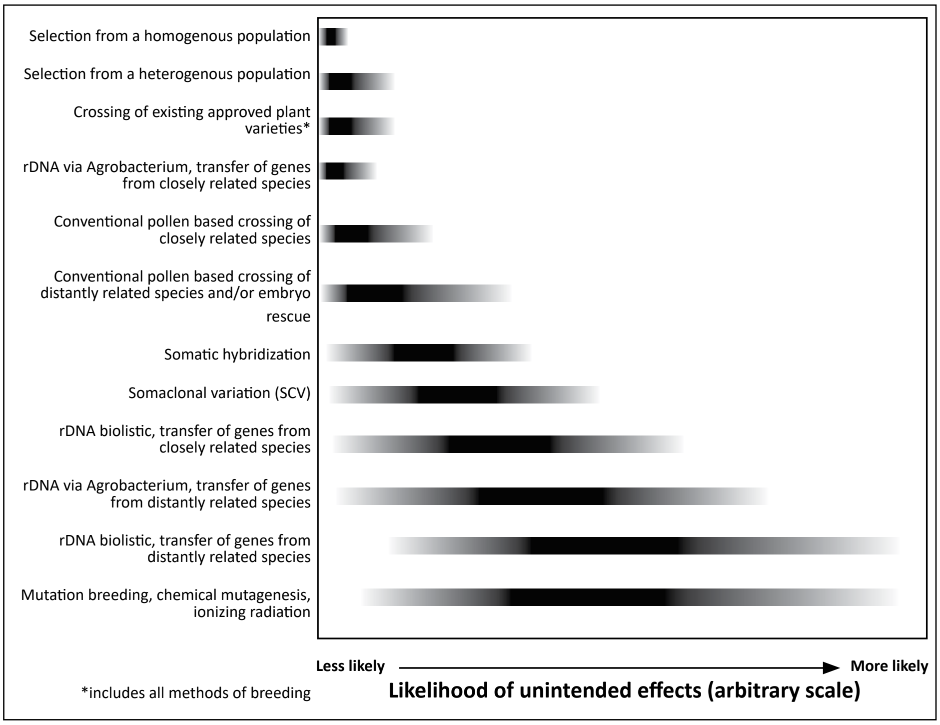

**Figure 1.** Likelihood of unintended effects from different breeding methods.
*Source: https://www.ncbi.nlm.nih.gov/books/NBK215778/*

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[17] Shu Q.Y., B.P. Forster, H. Nakagawa (2012) Plant Mutation Breeding and Biotechnology. CABI, USA, pp 55-58.

[18] Stadler, L.J. (1930) Some genetic effects of X-rays in plants. Journal of Heredity 21: 3-19 .

[19] IAEA. Mutant Variety Database. https://mvd.iaea.org/ Accessed on July 25, 2023

[20] Hartwell L. (2017) Genetics: From Genes to Genomes, 6th ed. New York, McGraw-Hill Education.

tification of desirable mutations is a long and labour-intensive process, and is generally a less effective approach to trait improvement in polyploid crops because of the significant genetic redundancy.

## 2.2 Advent of genome editing

In recent years, the ability to generate specific, useful mutations has been greatly advanced with the development of sequence-specific engineered endonucleases: the meganucleases, zinc finger nucleases (ZFNs), transcription activator-like effector nucleases (TALENs) and type II clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated protein 9 (Cas9), collectively referred as Site-Directed Nucleases (SDNs); also called programmable Sequence-Specific Nucleases (SSNs).

Genome editing is not new as early genome editing technologies have been used since the 1990s[21,22]. Initial genome editing technologies primarily used meganucleases and ZFNs, but these were technically complex and, thus, their application was limited to a few highly specialized laboratories. In 2011, Transcription Activator Like Effector Proteins Fused with Nucleases (TALENs) were developed. These were much simpler and were adopted by research groups for crop improvement[23]. Although their DNA binding domains differ, TALENs are structurally similar to ZFNs: both methods use the FokI nucleases to cut DNA and both require dimerization to function. TALENs showed improvement in genome editing technology and have been successfully used in multiple crops including rice, wheat, maize, tomato, soybean, sugarcane and potato, but the high labour and monetary cost still hinders its widespread adoption.

In 2012, the discovery of CRISPR-Cas9 has revolutionized genome editing. CRISPR-Cas9 has long been characterized in bacteria to help them fight off invading viruses. The first biochemical description of CRISPR was provided by Professors Jennifer Doudna and Emanuel Charpentier, who later won the Nobel Prize for chemistry in 2020 for the discovery. In 2013, Feng Zhang described how CRISPR could be used to edit eukaryotic DNA. Since then, there has been a rapid and unprecedent increase in use of this system for genome editing.

The CRISPR-Cas9 system consists of two key molecules that introduce a change into the DNA. An enzyme called Cas9 acts as a pair of 'molecular scissors' that can cut the two strands of DNA at a specific location in the genome so that bits of DNA can then be added or removed. The second, acting as a homing device, is a short molecule of RNA called guide RNA (gRNA) that consists of a small piece of pre-designed RNA sequence (about 20 bases long) located within a longer RNA scaffold. The scaffold part binds to DNA and the pre-designed sequence 'guides' Cas9 to the right part of the genome. This makes sure that the Cas9 enzyme cuts at the right point in the genome. The guide RNA is designed to find and bind to a specific sequence in the DNA, since the guide RNA has nucleotides complementary to the target DNA sequence in the genome.. The Cas9 follows the guide RNA to the same location in the DNA sequence and makes a cut across both strands of the DNA. At this stage the cell recognises that the DNA is damaged and tries to repair it. The human directed process ends, and the rest is achieved by the natural DNA repair mechanisms that exist in virtually all living cells. During the repair, there can be changes in the form of base deletions, insertions, or substitutions. Scientists can use the DNA repair machinery to introduce changes to one or more genes in the genome of a cell of interest. Although, single base deletions and insertions are the most frequent events, insertion or deletion of multiple bases also take place. Figure 2 explains the process in detail.

It is important to emphasize that not all sequences in the genome can be targeted by a single Cas nuclease, as the targeted sequence needs to be adjoining a 'Protospacer Adjacent Motif' (PAM). Several Cas9 variants have now been engineered to target virtually any sequence in the genome[24]. Different classes of CRISPR system are continuously being developed and used for crop improvement. For example, Cas12a (aka Cpf1) has

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[21] Rouet, P., F. Smihand M. Jasin(1994) Introduction of double-strand breaks into the genome of mouse cells by expression of a rare-cutting endonuclease. Molecular and Cellular Biology 14(12): 8096-8106 .

[22] Smih, F., P. Rouet, P. J. Romanienko and M. Jasin(1995) Double-strand breaks at the target locus stimulate gene targeting in embryonic stem cells. Nucleic Acids Research 23(24), 5012-5019 .

[23] Moscou, M.J. and A.J. Bogdanove (2009) A simple cipher governs DNA recognition by TAL effectors. Science 326 (5959): 1501.

[24] Zhan, X.Q., Lu, Y.M., Zhu, J.K.and Botella, J.R. Genome editing for plant research and crop improvement. Journal of Integrative Plant Biology 63, 3-33 (2021).

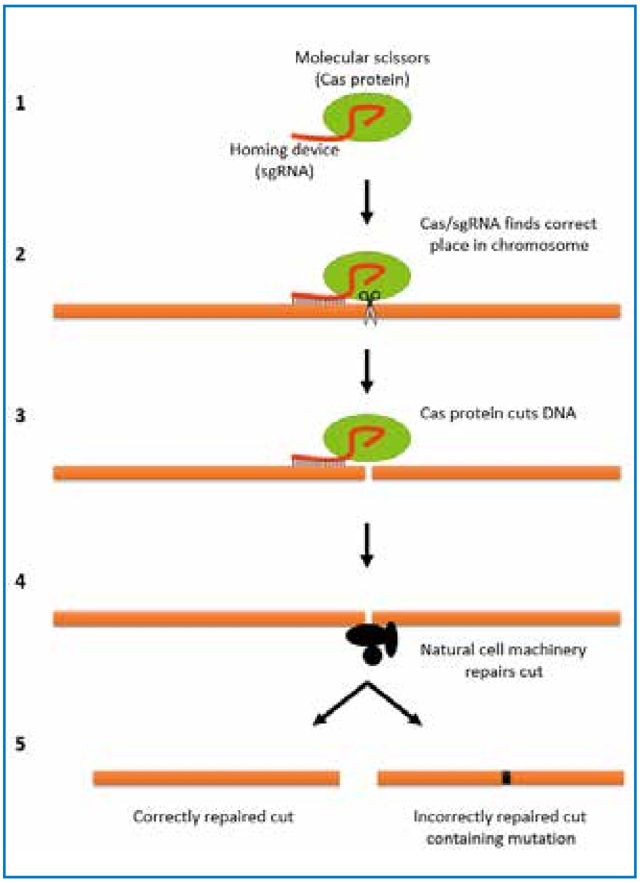

**Figure 2.** CRISPR/Cas mechanism of action.

*Source: Personal communication. Professor Jose (Jimmy) Botella, University of Queensland, Australia*

1. The CRISPR/Cas genome editing system contains two elements; a nuclease (Cas) that can cut double stranded DNA and a small molecule of RNA (sgRNA) that will guide the nuclease to the correct position in the chromosome. 2. The Cas/sgRNA complex uses the first 20 bases of the sgRNA to find the correct location in a chromosome by base complementarity. 3. Once the Cas/sgRNA complex locates the correct place, the Cas nuclease will perform a double strand break in the DNA. 4. The natural cellular repair machinery senses the break in the DNA and start the repair process. 5. The results of a 'correct' repair will restore the DNA to the original state. The result of an incorrect repair by the cellular machinery will produce a mutation in the DNA.

been progressively adopted for genome editing, as it favours T-rich PAMs, increasing the number of possible targets in the genome. Instead of forming blunt ends, Cas12a cleaves chromosomal DNA producing double-strand breaks (DSBs) with staggered ends[20]. Another variant Cas13 can bind single-stranded RNA molecules at specific sequences determined by the sgRNA. This system may be utilized to target RNA viruses[25].

In addition to the above methods that use proteins or proteins/RNA complexes to recognize DNA targets, it is also possible to create targeted modifications using short pieces of single- or double-stranded DNA (oligonucleotides)[26,27]. At some frequency, these oligonucleotides base pair with complementary sequences in the genome. If the oligonucleotide differs by one or a few bases from the genomic target sequence, a DNA mismatch repair mechanism is triggered. If the mismatch is repaired following the introduced oligonucleotide sequence, specific base modifications may be made in the genome. Oligonucleotide-directed mutagenesis (ODM) is, therefore, an alternative to nuclease-based genome editing.

Base editing is a relatively new method of genome editing derived from CRISPR-Cas9. Unlike traditional CRISPR systems, base editors (BEs) do not induce double-stranded breaks in the genome. It has emerged as a novel and efficient genome-editing approach which enables direct and irreversible conversion of one target base into another in a programmable manner. A base editor is a fusion of catalytically inactive CRISPR-Cas9 domain (Cas9 variants) and cytosine or adenosine deaminase domain that introduces desired point mutations in the target region, enabling precise editing of genomes. Cytidine deaminases (CDAs), which induce C to T substitutions, are naturally occurring in bacteria, while adenine deaminases (ADEs), which induce A to G substitutions, were engineered from bacterial enzymes specifically for base editing purpose.

In view of the limitations of the current cytocine base editor (CBE) or adenine base editor (ABE) systems, prime editing systems have been developed that allow for all possible transition mutations, as well as small insertions of up to 50 nucleotides and deletions of up to 80 nucleotides. Prime editing is a 'search-and-replace' genome-editing technology that introduces all base-to-

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[25] Shmakov, S., Abudayyeh, O.O., Makarova, K.S., Wolf, Y.I., Gootenberg, J.S., Semenova, E., Minakhin, L., Joung, J., Konermann, S., Severinov, K., Zhang, F.andKoonin, E.V. Discovery and Functional Characterization of Diverse Class 2 CRISPR-Cas Systems. Mol Cell 60, 385-397 (2015).

[26] Lusser, M., C. Parisi, D. Plan and E. Rodríguez-Cerezo (2011). New plant breeding techniques. Stateof-the-art and prospects for commercial development JRC Scientific and Technical Reports doi:10.2791/60346 EN.

[27] Sauer, N.J., J. Narváez-Vásquez, J. Mozoruk, R.B. Miller, Z.J. Warburg, M.J. Woodward, Y.A. Mihiret, T.A. Lincoln, R.E. Segami, S.L. Sanders and K.A. Walker (2016). Oligonucleotide-mediated genome editing provides precision and function to engineered nucleases and antibiotics in plants. Plant Physiology 170(4):1917-1928.

base conversions, as well as small insertions and deletions, without the need for DSBs or donor DNA templates. This system works using a Cas9 nickase, which induces single-stranded breaks in DNA, fused to a reverse transcriptase enzyme. The process of prime editing is described in Figure 3.

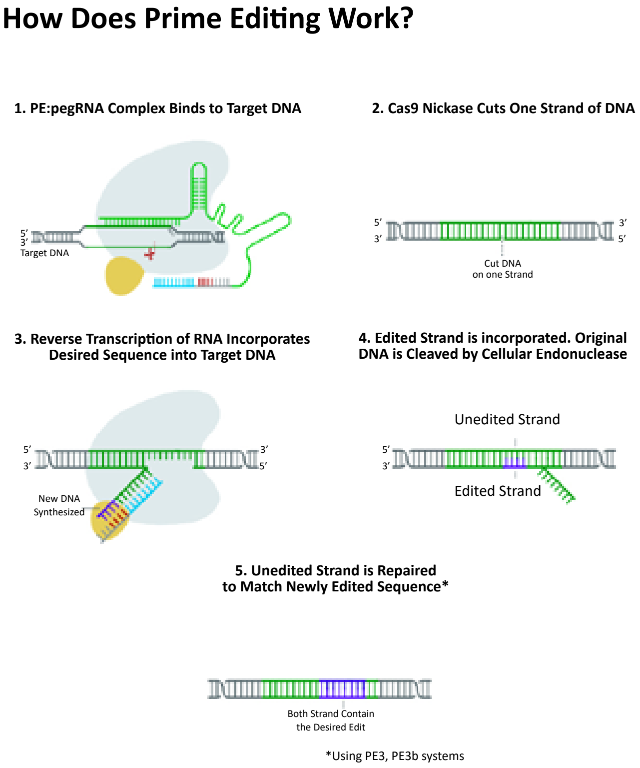

**Figure 3.** Prime Editing process.

*Source: https://www.synthego.com/guide/crispr-methods/prime-editing Accessed on July 25, 2023*

Base editing and prime editing are being applied in plants for precision breeding and can substantially expand the scope and capabilities of genome editing in plants. However, the current challenges regarding their editing efficiency are still under research and efforts are underway to improve and expand their use.

A challenge in plant genome editing is the efficient delivery of editing reagents to cells. Most methods of DNA delivery were developed decades ago with the intention of creating transgenic plants that express foreign genes incorporated into their genomes. Such transgenic plants are identified by their expression of marker genes that confer selectable or screenable traits. Unlike genetic engineering, stable transformation is not necessarily the objective of genome editing. Instead, the reagents are required only to persist in the cell long enough to achieve the desired editing outcome. In fact, incorporation of foreign DNA is often undesirable, particularly from a regulatory point of view.

Novel reagent delivery approaches have been developed that have enabled the delivery of DNA-free editing reagents. Such reagents invariably involve the use of ribonucleoproteins (RNPs), especially in the case of CRISPR/Cas9-mediated gene editing. In most of the non-DNA approaches, the recipient explant of choice is protoplasts. While the editing efficiency is high in protoplasts, the ability to regenerate individual plants from edited protoplasts remains a challenge. There are various innovative delivery approaches being utilized to perform in plant edits that can be incorporated in the germline cells or inherited via seed. With the modification and adoption of various novel approaches currently being used in animal systems, it is anticipated that non-transgenic genome editing will become routine in higher plants.

## 2.3 Types of genome editing created by SDNs

The generation of DSBs at specific sites in the plant genome (Figure 4) is the starting point for the most commonly used site-directed nucleases (SDNs). When this break is repaired via the host cellular repair mechanisms without the use of an added repair template, the approach is defined as SDN-1. The end result of SDN-1 is similar to a natural or induced mutation, except that instead of being random, the mutation occurs at a specific site in the genome. When a homologous repair template is added and the break is repaired via homologous recombination using this template, the approach is defined as SDN-2. The outcome of SDN-2 can be changes from one to a few base pairs and include the introduction of site-specific mutations. When the added template possesses DNA with homologous ends in combination with non-homologous sequences, and the break is repaired via homologous recombination using this template, then recombinant DNA is added to the genome and the approach is defined as SDN-3. Products of SDN-3 are conceptually similar to the products of genetic engineering with introduced transgenic or cisgenic sequences, except that the site of insertion is directed and specific.

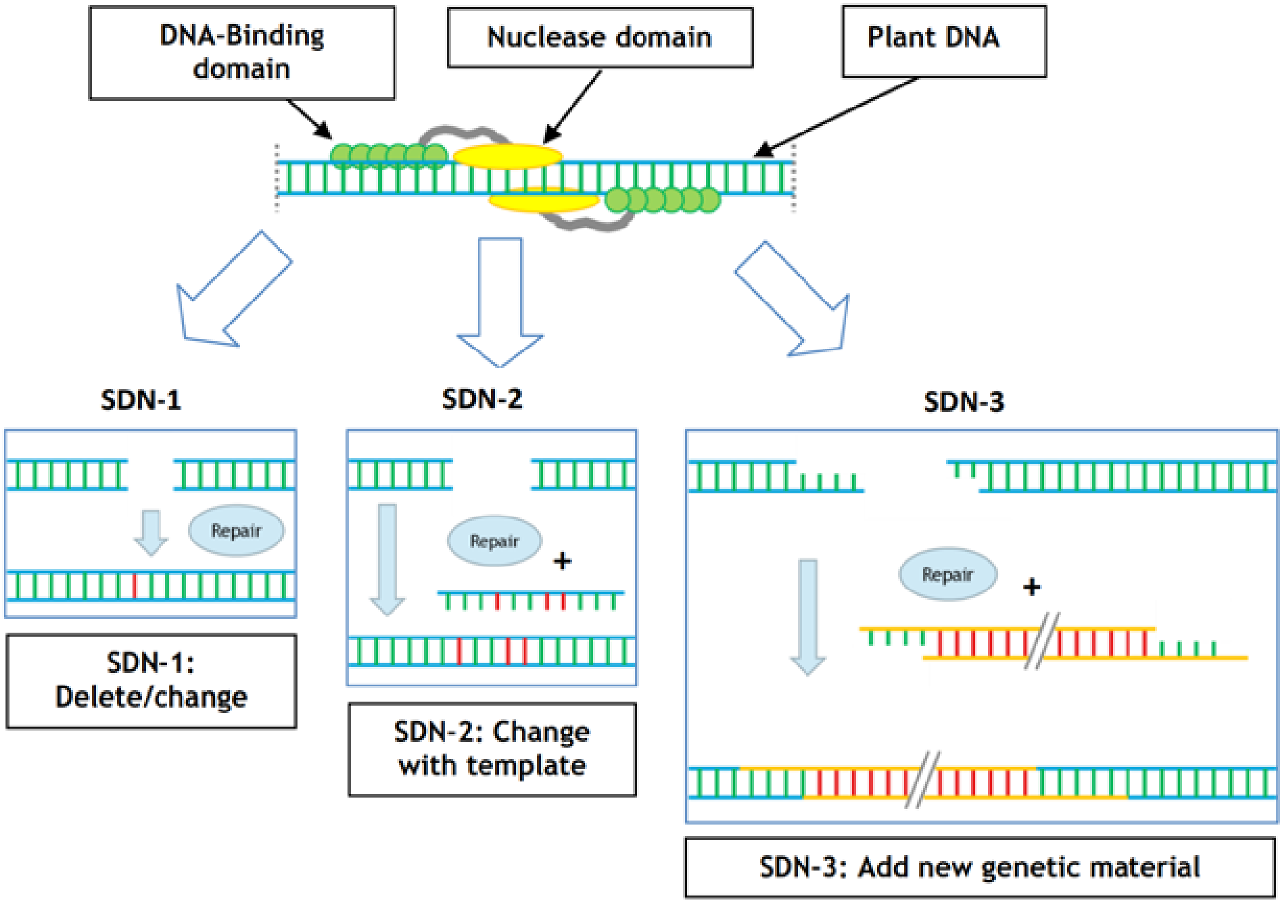

**Figure 4:** Types of genome editing

The definitions of SDN-1, SDN-2 and SDN-3 types of genome edited plants have been described by various authors. One of the commonly cited definitions adopted based on deliberations in a meeting by the Organization for Economic Co-operation and Development (OECD) held in 2018, are given in Box 1[28,29,30,31] :

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[28] Ricroch, A. (2019) Global developments of genome editing in agriculture. Transgenic Research 28 (2): 45–52

[29] Friedrichs, S., Y. Takasu, P. Kearns, B. Dagallier, R. Oshima, J. Schofield and C. Moreddu (2019) Meeting report of the OECD conference on “Genome Editing: Applications in Agriculture—Implications for Health, Environment and Regulation” Transgenic Research 28: 419–463.

[30] Friedrichs, S., Takasu, Y., Kearns, P., Dagallier, B., Oshima, R., Schofield, J., et al. (2019). Policy considerations regarding genome editing. Trends in Biotechnology, 37(10): 1029-1032.

[31] Friedrichs, S., Y. Takasu, P. Kearns, B. Dagallier, R. Oshima, J. Schofield and C. Moreddu (2019) An overview of regulatory approaches to genome editing in agriculture. Biotechnology Research and Innovation 3(2): 208-220.

### Box 1. Categories of genome editing

**SDN-1**: Techniques using site-directed nucleases with the objective of generating localized random base pair changes, deletions or short random insertions (indels), as a result of error in the cell gene repair mechanism based on non-homologous end joining (NHEJ). No exogenous DNA repair template is used in these applications.

**SDN-2**: Techniques using site-directed nucleases with the objective of generating a localized pre-defined point mutation or deletion/addition, because of co-introducing a repair DNA molecule that is homologous to the targeted area and is expected to act as a repair template. Repairing is achieved by homologous recombination (HR). SDN-2 generates changes spanning few base pairs in genetic elements (promoters, coding sequences, etc.) that pre-exist in the host genome.

**SDN-3:** Techniques using site-directed nucleases with the objective of generating a localized pre-defined insertion/deletion/replacement of entire genetic elements (promoters, coding sequences, etc.), or entire genes, because of co-introducing a large DNA molecule to be inserted in the target area. DNA molecule may or may not be homologous to the targeted area, and its insertion can take place either by HR or by NHEJ.

## 2.4 Applications of genome editing in plants

In view of its precision and efficiency, genome editing has the potential to have a large, positive impact on plant agriculture[32,33,34,35]. For example, gene knockouts are possible for every crop provided reagents can be introduced and the plant subsequently regenerated. This includes knocking out genes present in multiple copies in a genome or across the multiple genomes present in polyploid plants. In contrast to random mutagenesis, it causes relatively few or no mutations at unintended sites in the genome and therefore obviates the need to perform extensive crosses to remove unwanted mutations. Further, genome editing allows knowledge-based alterations in a plant's genome, as compared to conventional breeding in which large populations with natural or artificially induced genetic variation are screened for desired trait or traits. By using genome editing, even multiple mutations are possible within a desired genetic background in a single step.

Even though the genome editing technologies are quite recent, there are numerous examples of the use of genome editing in plants under active research programs for the benefit of farmers and consumers. Important agronomic traits such as yield, resistance to diseases, resistance to stresses such as heat and drought have been improved using genome editing. In addition, consumers can now benefit from more nutritious foods, reduced amounts of unhealthy chemicals and improved flavour in genome edited crops.

The first gene edited plant to be commercialized were a high oleic acid soybean variety in USA followed by high Gamma-Aminobutyric Acid (GABA) tomato in Japan.

**High oleic soybean:** As two genes involved in fatty acids synthesis have been turned off, resulting soybean oil has 80% higher oleic acid, 20% less saturated fatty acids and 0 gram trans-fat per serving. It is claimed to have three times the fry-life and a longer shelf-life compared to the current soybean oil being sold in the market.

**High GABA tomato:** High GABA tomato contains around five to six times the normal level of a type of amino acid called GABA. This was achieved by clipping out one of the tomato's genes that inhibits the synthesis of GABA. It is expected to help in lowering blood pressure.

Some other products that have been cleared by the regulators in various countries include varieties of mushroom, canola, rice, *etc*.

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[32] Belhaj, K., A. Chaparro-Garcia, S. Kamoun, N.J. Patron and V. Nekrasov (2015) Editing plant genomes with CRISPR/Cas9. Current opinion in biotechnology 32: 76-84.

[33] Montenegro, M (2016) CRISPR is coming to agriculture—With big implications for food, farmers, consumers and nature. Ensia http://ensia.com/voices/crispr-is-coming-to-agriculture-with-big-implications-for-food-farmers-consumers-and-nature/ Accessed on July 25, 2023

[34] Quétier, F. (2016) The CRISPR-Cas9 technology: Closer to the ultimate toolkit for targeted genome editing. Plant Science 242: 65–76

[35] Song, G., M. Jia, K. Chen, X. Kong, B. Khattak, C. Xie, A. Li and L. Mao (2016) CRISPR/Cas9: A powerful tool for crop genome editing. The Crop Journal 4 (2): 75–82

**Non-browning mushroom:** White button mushroom (*Agaricus bisporus*) has been modified with small deletions in a specific polyphenol oxidase gene with no foreign DNA integration into the mushroom genome. The anti-browning trait reduces the formation of brown pigment (melanin), improving the appearance and shelf life of mushroom, and facilitating automated mechanical harvesting.

**High oil containing canola:** Canola with increased oil content in seeds has been developed by activating a negative regulator of the enzyme acetyl-CoA carboxylase (ACCase), the key enzyme for producing fatty acids for oil biosynthesis. Reducing activity of the regulator protein has resulted in significantly increased oil content in seeds.

**Bacterial blight resistant rice:** Gene-edited rice has been developed by disrupting the function of promoters for sugar transport genes critical for plants susceptibility to infection by *Xanthomonas* Oryza resulting in resistance to bacterial blight.

**Semi-dwarf teff:** Gene-edited teff has been developed with an objective to prevent lodging problem in teff and improving the grain productivity. The gene (SD-1) responsible for the semi-dwarf phenotype was targeted.

Many other improved crops are in various stages of development using gene editing techniques. Attempts have been made to collate information on the research studies underway for development of genome edited plants[36,37]. Meanwhile, several efforts in crop gene editing have been undertaken to improve performance across a range of crops and traits. Climate resilience, heat- and cold-tolerance, rain-resistance, disease resistance, weed resistance, nutritional enhancement, reduced allergenicity and yield performance are among the traits being improved or introduced in various crops[38,39,40]. To facilitate a more comprehensive understanding of the use of genome editing, "European Sustainable Agriculture through Genome Editing" Organization (EU-SAGE) has developed a publicly accessible online database of genome-edited crop plants as described in peer-reviewed scientific publications (https://www.eu-sage.eu/). The database includes research on crop plants wherein the introduced traits are relevant from an agricultural and/or food/feed perspective[41]. The database is regularly updated and information is classified on the basis of trait categories, countries, crops, types of techniques used and outcome in terms of type of genome editing. A summary of the information available on EU-SAGE, as accessed on June 27, 2023 is presented in the figures below:

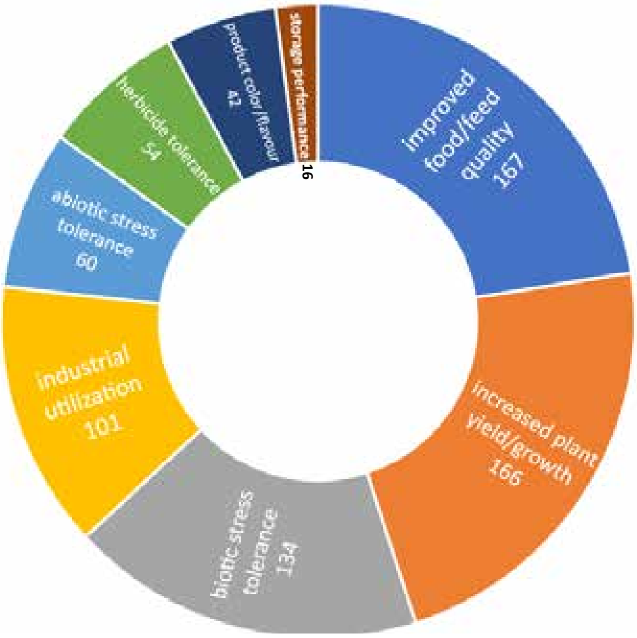

**Figure 5:** Trait categories studied using gene editing

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[36] Modrzejewski, D., F. Hartung, T. Sprink, D. Krause, C. Kohl and R. Wilhelm (2019). What is the available evidence for the range of applications of genome-editing as a new tool for plant trait modification and the potential occurrence of associated off-target effects: a systematic map. Environmental Evidence 8(1):1-33

[37] Menz, J., D. Modrzejewski, F. Hartung, R. Wilhelm and T. Sprink (2020) Genome edited crops touch the market: a view on the global development and regulatory environment. Frontiers in Plant Science 11: 586027

[38] Karavolias N.G. (2021) Application of gene Editing for climate change in agriculture. Frontiers in Sustainable Food System 5: 685801

[39] Smyth S.J. (2022) Contributions of genome editing technologies towards improved nutrition, environmental sustainability and poverty reduction. Frontiers in Genome Editing 4: 863193

[40] Mbaya, H., S. Lillico, S. Kemp, G. Simm and A. Raybould (2022) Regulatory frameworks can facilitate or hinder the potential for genome editing to contribute to sustainable agricultural development. Frontiers in Bioengineering and Biotechnology 10: 959236

[41] Database of genome-edited crop plants by European Sustainable Agriculture Through Genome Editing (EU-SAGE). https://eu-sage.eu/genome-search. Accessed on July 15, 2023

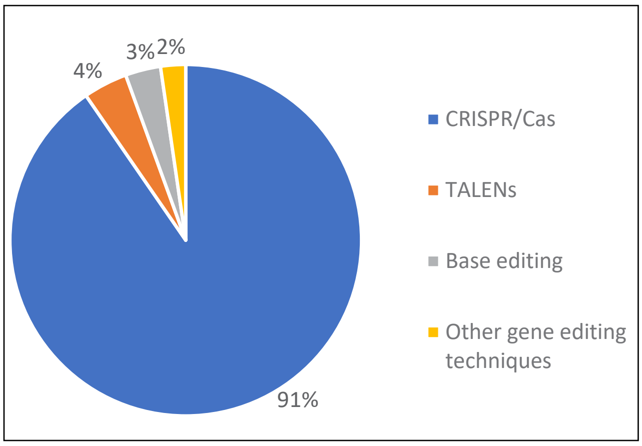

**Figure 6:** Gene editing techniques used

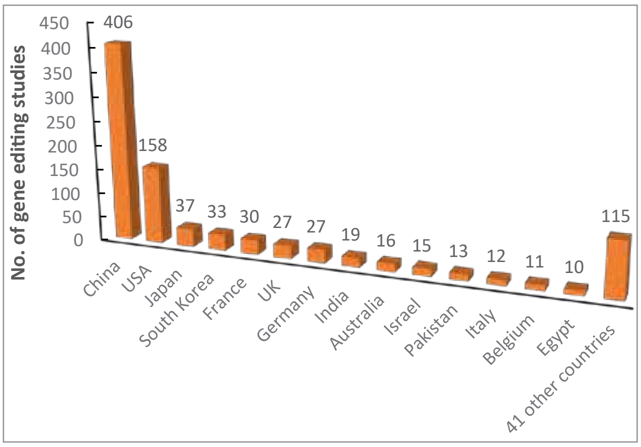

**Figure 7:** Countries where gene editing studies were conducted

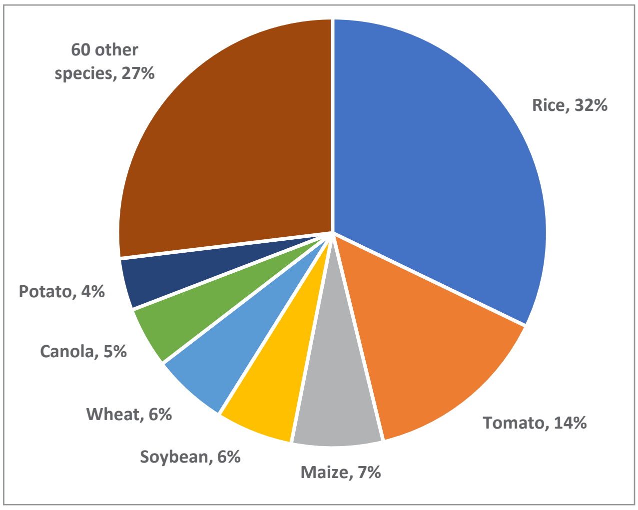

**Figure 8:** Percentage of gene editing studies on major crops

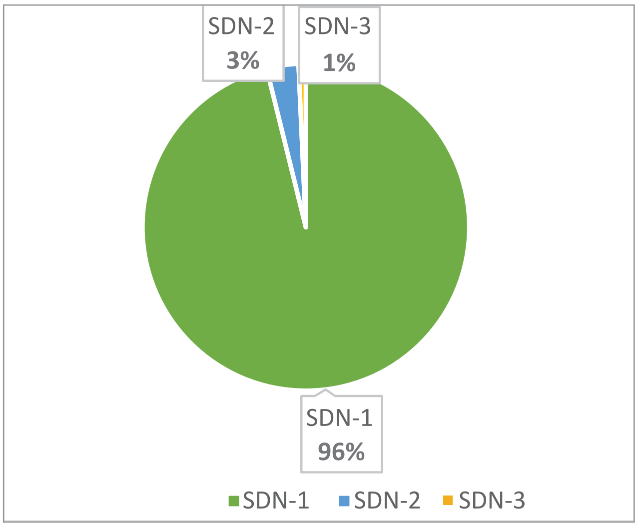

**Figure 9:** Types of gene editing outcome

New and exciting developments are being published virtually every week. Table 1 provides a glimpse of some applications of gene editing technologies for agrifood systems in research institutions, as summarized in a recent report by FAO[42].

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[42] FAO (2022) Gene editing and agrifood systems. Rome. https://doi.org/10.4060/cc3579en.

**Table 1 : Applications of gene editing technologies in agrifood systems**

| Plant | Trait | Research organization |
|---|---|---|
| **Improved food and feed quality** | | |
| Camelina | Improved fatty acid composition | Department of Plant Sciences and Plant Pathology, Montana State University, Bozeman, MT 59717, USA |
| Lettuce | Increased vitamin C content | State Key Laboratory of Plant Cell and Chromosome Engineering, Center for Genome Editing, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China |
| Oilseed rape | Improved fatty acid composition | National Key Laboratory of Crop Genetic Improvement, Huazhong Agricultural University, Wuhan, China |
| Potato | Reduced acrylamide formation | Cellectis plant sciences Inc., New Brighton, MN, USA |
| Soybean | Improved fatty acid composition | Calyxt, Roseville, MN, USA |
| Tomato | High content of γ-aminobutyric acid (GABA) | Sanatech Minato-ku, Tokyo, Japan & University of Tsukuba, Ibaraki, Japan |
| Wheat | Low gluten content | Instituto de Agricultura Sostenible (IAS-CSIC), Córdoba, Spain |
| | | Wageningen University, Wageningen, Netherlands |
| Wild tomato | *De novo* domestication – High antioxidant content | Several universities from Brazil, Germany and the USA |
| Brewer’s yeast | Flavour improvement in fermented beverages | Centre of Microbial and Plant Genetics, Leuven, Belgium |
| **Improved agronomic properties** | | |
| Alfalfa | High yield | National Institute of Agricultural Technology, Argentina |
| Banana | Fungus protection | Queensland University of Technology, Brisbane, Australia |
| | Protection against bacterial wilt, fusarium wilt and banana streak virus | International Institute of Tropical Agriculture, Nigeria |
| | Protection against bunchy top virus | Agricultural Research Council, Pretoria, South Africa |
| Cacao | Protection against fungal disease | Pennsylvania State University, USA |
| Cassava | Reduced cyanide levels | University of California, Berkeley, CA, USA |
| | Virus resistance | |
| Cherry | Virus resistance | Department of Horticulture, Plant Biotechnology Resource and Outreach Center, Michigan State University, East Lansing, MI, USA |
| Citrus | Protection against citrus canker | Chinese Academy of Sciences, China |
| Cucumber | Protection against multiple viruses | Department of Plant Pathology and Weed Research, ARO, Volcani Center, Bet-Dagan, Israel |
| Flax | Herbicide tolerance | Cibus, San Diego, CA, USA |
| Grapevine | Drought tolerance | Stellenbosch University, Stellenbosch, South Africa |
| Maize | Fungus resistance | DuPont Pioneer, Johnston, IA, USA |
| Oilseed Rape | Herbicide tolerance | Key Laboratory of Plant Functional Genomics of the Ministry of Education, Yangzhou University, Yangzhou China |
| Potato and sugar beet | Disease-resistant varieties | Russian Academy of Sciences, Russian Federation |
| Rice | Salt tolerance | National Institute for Plant Biotechnology, New Delhi, India |
| | Fungus protection | Department of Genetics, Development & Cell Biology, Iowa State University, Ames, Iowa, USA |

| Plant | Trait | Research organization |
|---|---|---|
| | Salt tolerance | Key Laboratory of Rice Genetic Breeding of Anhui Province, Rice Research Institute, Anhui Academy of Agricultural Sciences, Hefei, 230031, China |
| Sorghum | Increased protein content | University of Queensland, Queensland, Australia |
| | Striga resistance | Kenyatta University, Kenya |
| Soybean | Nematode resistance | Evogene, Rehovot, Israel & TMG, Cambé, Brazil |
| Tomato | Bacterial resistance | Department of Plant and Microbial Biology, University of California, Berkeley, USA |
| | Provitamin D3 enhanced | John Innes Centre, Norwich, United Kingdom |
| Wheat | Fungus protection | State Key Laboratory of Plant Cell and Chromosome Engineering, Institute of Genetics and Developmental Biology, Chinese Academy of Sciences, Beijing, China |

## 2.5 Conclusions

Gene editing is built on scientific advances and better understanding of natural processes. As is evident from above, there has been enormous progress in the development and applications of genome editing in plants. Genome editing provides a unique tool to improve the livelihood of farmers, deliver huge environmental benefits and provide healthier and more nutritious foods to humankind, both in the developed world as well as the developing economies. The precision of genome editing, compared to the available commercial technologies such as random mutagenesis is astonishing and it is translated into shorter development times for breeding, lower costs of development and higher quality of the final products. Gene editing is expected to play a major role in breeding new crop varieties with much improved characteristics, and more products of this breeding approach may be anticipated in the near future.

# CHAPTER 3
# EXISTING AND EMERGING POLICIES FOR GENOME EDITED PLANTS

## 3.1 Introduction

The increasing application of genome editing in crop improvement requires the development of policy that will enable the products of this technology to move forward and be of benefit to farmers and consumers. The regulations for genome edited plants are evolving globally. The evolution of regulatory approaches is based on the recognition of the similarity between gene edited and conventionally bred plants, vis-à-vis genetically modified organisms (GMOs). The current regulatory status of genome edited plants in countries where policies are already implemented and the status of emerging regulations in countries of the Asia-Pacific region, where the discussions are underway, are presented in this chapter. An overview of ongoing deliberations at international fora is also included.

## 3.2 Regulatory approaches in various countries

Various countries have notified approaches to be followed for different types of genome editing in plants through amendments in their regulations and /or issuance of new guidelines. Current status of genome editing legislation (up to July 2023) in various countries is depicted in Figure 10[43] and a brief overview of selected countries/regions is given below.

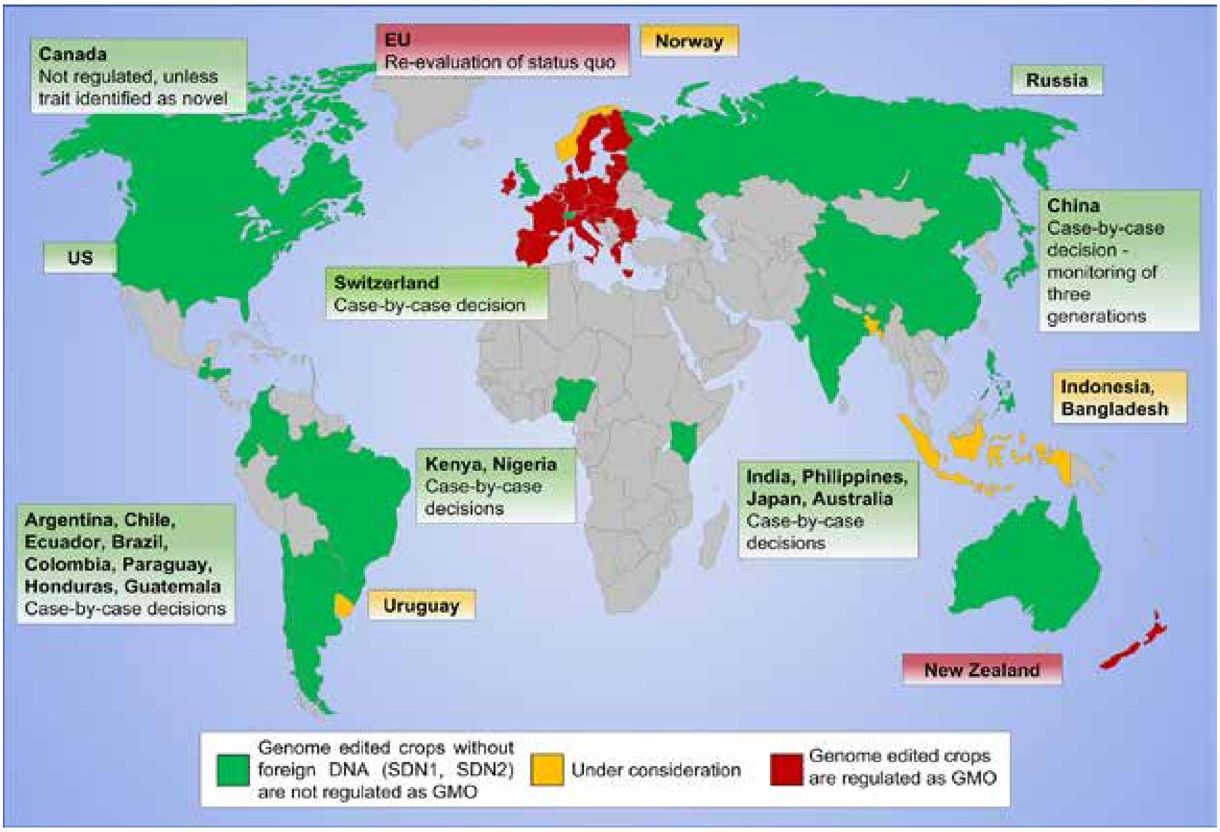

**Figure 10.** Current status of genome editing legislation in various countries

*Source: Buchholzer, M. and W.B. Frommer (2023)*

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[43] Buchholzer, M. and W.B. Frommer (2023) An increasing number of countries regulate genome editing in crops. New Phytologist 237(1): 12-15.

## 3.3 South American countries

Argentina was the first country to adopt a new regulation, specifically addressing new breeding techniques (NBTs), including genome editing. In 2015, Resolution 173[44] was issued by Ministry of Agriculture, Livestock and Fisheries of Argentina (MAGyP) to establish procedures to establish the criteria for determining whether or not a variety developed by modern biotechnology would fall under its GMO regulations. To this end, applicants submit a description of each NBT-derived crop or product to establish whether or not the breeding process results in a new combination of genetic material. The new regulatory approach indicated that:

- If the NBT-derived crop does not have a new combination of genetic material (e.g. does not use a transgene/uses a transgene which is removed in the final product), a non-GM regulatory classification is applied thereon:
- If the NBT has a new combination of genetic material (e.g. uses a transgene which remains in the final product), the regulatory classification stipulates that the final product falls under GM category.

An interesting feature of the regulation is the option for developers to present their projects ‘‘at design stage’’ and consult with regulators to confirm that they have produced a genome edited plant.[45] Thus, the process can be applied to both real products and hypothetical products (Figure 1)[46]. Basic information on the overall breeding process, genetic changes, traits, bred-out of helper transgenes, etc. is required.

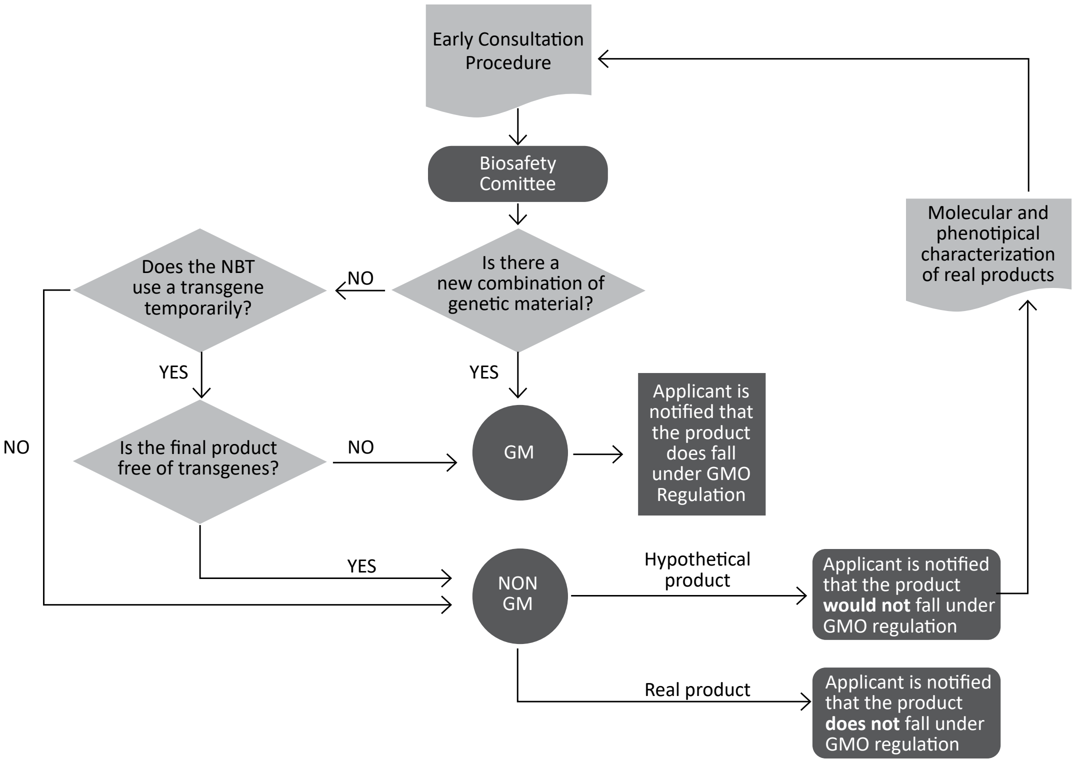

**Figure 11:** Roadmap for the regulatory classification of new breeding techniques, including gene-edited crops, in Argentina.
*Source: Whelan, A. I., and M.A. Lema (2019)*

The approach by Argentina of making regulatory decisions based on the presence or absence of foreign genes has also been adopted by other South American countries viz. Brazil, Chile, Paraguay, Colombia, Honduras, Ecuador, and Guatemala, although, there are some minor differences in guidelines of different countries within the region.[47,48] Regulatory guidelines are still under consideration by Uruguay.

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[44] Whelan A.I. and M.A. Lema (2015) Regulatory framework for gene editing and other new breeding techniques (NBTs) in Argentina. GM Crops Food. 6(4):253-65
[45] Lema, M. A. (2019). Regulatory aspects of gene editing in Argentina. Transgenic Research, 28( 2): 147-150
[46] Whelan, A. I., and M.A. Lema (2019) Regulation of genome editing in plant biotechnology: Argentina. In: Dederer, HG., Hamburger, D. (eds). Regulation of Genome Editing in Plant Biotechnology: A Comparative Analysis of Regulatory Frameworks of Selected Countries and the EU. Springer, Cham.Switzerland, pp 19-62
[47] Kuiken, T. and J. Kuzma (2021) Genome Editing in Latin America: Regional Regulatory Overview. Inter-American Development Bank, Rural Development and Disaster Risk Management Division: Discussion Paper No. IDB-DP-00877. https://research.ncsu.edu/ges/files/2021/08/Kuzma-Reg-IDB_Final_July2021.pdf. Accessed on July 25, 2023
[48] Buchholzer M. and W.B. Frommer (2022) An increasing number of countries regulate genome editing in crops. New Phytologist 237(1): 12-15

## 3.4 African countries

Nigeria's National Biosafety Management Agency (NBMA) issued its guidelines for crop gene editing on December 2020, making Nigeria the first country in Africa to address the issue of gene edited crops[49]. The guidelines stated that when gene editing of a product does not lead to a new combination of genetic material (as happens with GM transgenics), a new case-by-case regulatory provision leading to issuance of Biosafety Approval (Clearance) would apply. If however the gene editing of the product leads to a new combination, it would be identified as ''GMO'', the National Biosafety Regulations 2017 would apply.

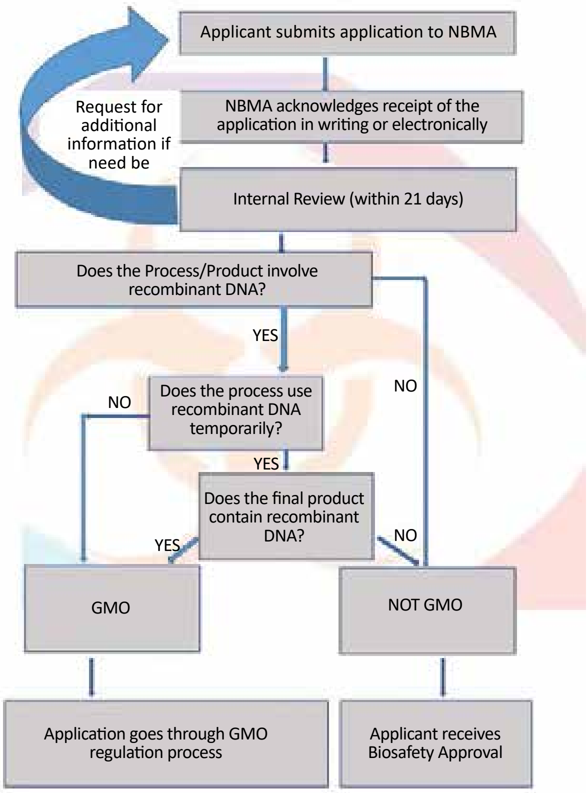

**Figure 12:** Flow Chart for Regulation of Gene Editing in Nigeria

*Source: https://nbma.gov.ng/wp-content/uploads/2022/03/NATIONAL-GENE-EDITING-GUIDELINE.pdf*

After Nigeria, Kenya became the second country in Africa to develop guidelines for genome editing not only for plants but also for animals. Kenya's National Biosafety Authority published guidelines in February 2022 to facilitate the research and development of gene-edited plants and animal products[50]. The Guidelines outline considerations to determine whether or not the genome editing techniques and derived products would be regulated under the country's Biosafety Act. Genome editing and derived products that will not be regulated under the Biosafety Act include; modifications made by inserting genes from sexually compatible species, deletions/knockouts without foreign genetic material in the end-product, and processed products whose inserted foreign genetic material cannot be detected. It provides for early consultation to determine the regulatory pathway and case-by-case decisions.

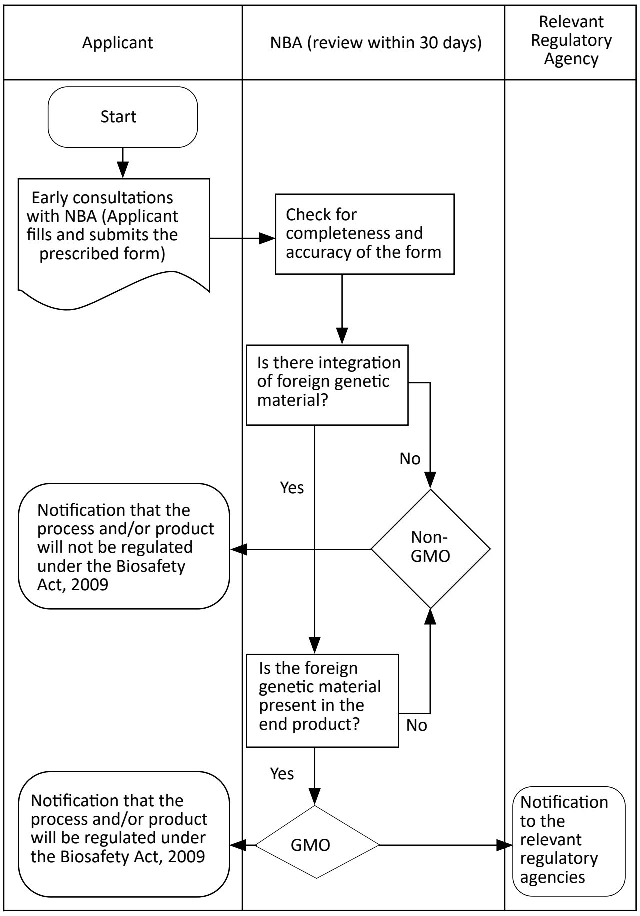

**Figure 13:** Flow Chart for the Early Consultation on genome editing processes in Kenya

*Source: https://www.biosafetykenya.go.ke/images/GENOME-EDITING-GUIDELINES-FINAL-VERSION-25th-Feb-2022-03.pdf. Accessed on July 25, 2023*

Some other countries in Africa are still in the process of developing genome editing policies while Eswatini and Burkina Faso have prepared policy drafts.[51,52]

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[49] National Biosafety Management Agency (2020) National Biosafety Guidelines on Gene Editing https://nbma.gov.ng/wp-content/uploads/2022/03/NATIONAL-GENE-EDITING-GUIDELINE.pdf

[50] National Biosafety Authority: Guidelines for Determining the Regulatory Process of Genome Editing Techniques in Kenya (2022). https://www.biosafetykenya.go.ke/images/GENOME-EDITING-GUIDELINES-FINAL-VERSION-25th-Feb-2022-03.pdf. Accessed on July 25, 2023

[51] Alliance for Science (2021) Three African Nations Take the Lead in Agricultural Use of Genome Editing. https://allianceforscience.cornell.edu/blog/2021/01/three-african-nations-take-the-lead-in-agricultural-use-of-genome-editing/. Accessed on July 25, 2023

[52] AUDA-NEPAD (2021) Technical Support Development of Guidance Document Genome Editing Burkina Faso. https://www.nepad.org/news/technical-support-development-of-guidance-document-genome-editing-burkina-faso. Accessed on July 25, 2023

## 3.5 Australia

In Australia, GMOs are regulated by the Office of Gene Technology Regulator (OGTR) as per the Gene Technology Act 2000 (GT Act) and Gene Technology Regulations 2001 [53,54].

These regulations provide broad, overarching definitions of ‘gene technology’ and ‘GMO’ to be regulated in Australia and also provides for exclusions and inclusions[55,56]. A technical review of the GT Regulations was initiated in 2016 in light of ongoing technical progress with plant breeding innovations that includes genome editing. The Australian government officially published a set of updated amendments of the GT Regulations in April 2019[57], indicating that SDN-1 organisms are not GMOs provided that: i) no nucleic acid template was added to cells to guide genome repair after site-directed nuclease application; and ii) the organism has no other traits from the gene technology (e.g. cas9 transgene, expressed SDN protein). It has also been stated that no confirmation is required for exemptions from the regulations and developers can self-determine compliance with the requirements. The discussions on additional exemptions are underway.

Regarding food safety issues, Food Standards Agency of Australia New Zealand (FSANZ) has also initiated the process of revisions of food standards, which define GM foods. The proposal under discussion is to exempt certain products based on product-based criteria. These include food from which foreign gene have been removed, food with characteristics that can be produced by conventional breeding and processed food that does not contain foreign genes or new proteins. Efforts are underway to update the definitions to make them clearer and better able to accommodate food produced by existing, emerging, and future genetic technologies. The final decision is expected in near future[58].

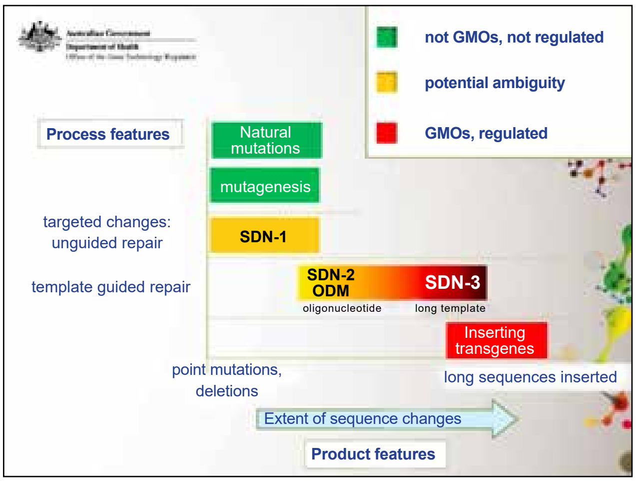

**Figure 14**: Regulations for gene editing in Australia
*Source: Thygesen, P. (2021)*

## 3.6 Canada

In Canada all plant products, whether obtained through conventional breeding including classical mutagenesis or biotechnology are subject to the same oversight based on novelty of product characteristics referred to as “plants with novel traits (PNTs)”. A PNT is defined as “a plant containing a trait not present in plants of the same species already existing as stable, cultivated populations in Canada, or is present at a level significantly outside the range of that trait in stable, cultivated populations of that particular plant species in Canada”. There is no clear definition of novelty, but a rule of thumb of about 20% difference in the respective trait(s) to a reference product has been established.[59] Health Canada in 2022 have issued guidelines/notifications confirming that gene-edited crops that meet the categories set for food that is not considered novel food can be treated like conventional crops, and would not be required to go through the pre-market safety evaluation applied for GM crops.[60] Recently in 2023, Canadian Food Inspection Agency (CFIA) updated its guidance for seed regulations and confirmed that since gene editing can be used to accomplish genetically identical outcomes to what would

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[53] Commonwealth of Australia (2000) Gene Technology Act 2000. The Federal Register of Legislation at https://www.legislation.gov.au/Details/C2016C00792. Accessed on July 25, 2023

[54] Commonwealth of Australia (2001) Gene Technology Regulations 2001. The Federal Register of Legislation at https://www.legislation.gov.au/Details/F2016C00615. Accessed on July 25, 2023

[55] Thygesen, P. (2019) Clarifying the regulation of genome editing in Australia: situation for genetically modified organisms. Transgenic Research 28(2): 151-159.

[56] Thygesen, P. (2021) Presentation on Regulation of Genome Edited Organisms-OECD, and other international & regulatory perspectives. Webinar on Advancing Genome Edited Plants from Lab to Land, Asia-Pacific Association of Agricultural Research Institution (APAARI)

[57] Australian Government Federal Register of Legislation. https://www.legislation.gov.au/Details/F2019L00573/Explanatory%20Statement/Text (Accessed on July 25, 2023)

[58] Food Standards Australia New Zealand (FSANZ): Proposal P1055.
https://www.foodstandards.gov.au/code/proposals/Pages/p1055-definitions-for-gene-technology-and-new-breeding-techniques.aspx (Accessed on July 25, 2023)

[59] Smyth, S. J. (2017). Canadian regulatory perspectives on genome engineered crops. GM Crops & Food 8(1): 35-43

[60] Health Canada: Guidelines for the Safety Assessment of Novel Foods. https://www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidelines-safety-assessment-novel-foods-derived-plants-microorganisms/guidelines-safety-assessment-novel-foods-2006.html#a5 (Accessed on July 25, 2023)

be achievable using conventional breeding practices, gene-edited plant products should be regulated like all other products of plant breeding, namely, by the traits they exhibit and how these traits impact the safety of environmental and human health[61].

## 3.7 European Union

In a lawsuit over the legal status of genome editing technology, the European Court of Justice (CJEU) in 2018[62] did not permit exemption of genome editing as part of mutation breeding methods listed in the Directive 2001/18/EC and therefore genome editing continues to be treated as GMO in the European Union.

Subsequently, in 2021, the European Commission (EC) has published a study regarding the status of new genomic techniques (NGTs) under Union Law. The study has concluded that for certain NGTs viz. SDN-1, SDN-2, Oligonucleotide-directed mutagenesis (ODM) and cisgenesis, no new hazards have been identified compared to both conventional breeding and established genomic techniques (EGTs), and hence concluded that the current GMO legislation, adopted in 2001, is not fit for purpose for certain NGTs and their products, and that it needs to be adapted to scientific and technological progress (European Commission, 2021)[63] .

On July 5, 2023, the European Commission has proposed a Regulation of the European Parliament and of the Council on plants obtained by certain new genomic techniques (NGTs) and their food and feed, and amending Regulation (EU) 2017/625 by revising its rules on GMOs. The proposal creates two distinct pathways for NGT plants to be placed on the market.

NGT plants that could also occur naturally or by conventional breeding will be subject to a verification procedure, based on criteria set in the proposal. NGT plants that meet these criteria are treated like conventional plants and, therefore, exempted from the requirements of the GMO legislation. This means that for these plants no risk assessment has to be made and they can be labelled in the same way as conventional plants.

For all other NGT plants, the requirements of the current GMO legislation would apply. This means that they are subject to risk assessments, and they can only be put on the market following an authorisation procedure. For these plants there will be adapted detection methods and tailored monitoring requirements.

The proposal needs approval from the European Parliament and EU governments and may be revised[64,65]. After approval, new proposal will facilitate to study and commercialize the gene-edited plants/crops in several European countries.

## 3.8 Israel

In Israel, National Committee for Transgenic Plants (NCTP)[66] published the decision in March 2017 that genome edited plants resulting only in a deletion of nucleotides and with no insertion of foreign DNA, are not considered to be transgenic and will not be subjected to the Seed Regulation of Plants and other GE Organisms 2005 (GE Seed Regulation). The applicants are required to submit data showing that they meet the determined criteria to ensure that foreign DNA sequences were not incorporated into a plant genome. Regarding other genome edited plants, where foreign DNA is incorporated, their progeny will be subjected to regulations and guidelines in accordance with the GE Seed Regulation.

In March 2019, the NCTP reconfirmed its previous decision that plants which are progeny of plants that under-

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[61] Canadian Food Inspection Agency: Rationale for updated guidelines for determining whether a plant is regulated under Part V of the Seeds Regulations (Directive 2009-09)https://inspection.canada.ca/plant-varieties/plants-with-novel-traits/applicants/directive-2009-09/rationale-for-updated-guidelines/eng/1682425597052/1682425597973 (Accessed on July 25, 2023)

[62] European Court of Justice (2018) Judgment of 25 July 2018, Confédération Paysanne a.o., C- 528/16. ECLI:EU:C:2018:583. https://curia.europa.eu/juris/liste.jsf?language=en&num=C-528/16 (Accessed on June 24, 2023)

[63] European Commission (2021) Commission Staff Working Document. Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16. Brussels, SWD(2021) 92 final.

[64] https://food.ec.europa.eu/document/download/5135278b-3098-4011-a286-a316209c01cd_en?filename=gmo_mod-bio_ngt_eu-study.pdf (Accessed on June 24, 2023) https://ec.europa.eu/commission/presscorner/detail/en/qanda_23_3568

[65] Stokstad, E. (2023, July 7) European Commission proposes loosening rules for gene-edited in plants. Science https://www.science.org/content/article/european-commission-proposes-loosening-rules-gene-edited-plants?utm_source=sfmc&utm_medium=email&utm_campaign=WeeklyLatestNews&utm_content=alert&et_rid=428337117&et_cid=4805948. Accessed on June 24, 2023

[66] USDA FAS GAIN Report (2021) Agricultural Biotechnology Annual. GAIN Report Number: IS2021-0011 https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=Agricultural%20Biotechnology%20Annual_Tel%20Aviv_Israel_10-20-2021.pdf. Accessed on June 24, 2023

went "targeted mutagenesis" utilizing genome editing methodology do not fall under the category of transgenic plants and will not be subjected to GE Seed Regulation if i) only a deletion of nucleotides occurred; ii) no inserted or incorporated foreign DNA is present in the plant genome.

## 3.9 United Kingdom

In March 2023, Genetic Technology (Precision Breeding) Act has been approved in England that distinguishes between transgenic GMOs in which genes from another species are used in development versus gene edited changes, which could have occurred naturally or by traditional breeding methods. The Act provides a framework for subsequent implementing rules to be introduced through secondary legislation in the country[67]. The Act applies to precision bred plants and vertebrate animals (excluding humans), meaning they are gene edited, and would remove them from the regulatory system for GMOs.

The Act has the powers to remove plants and animals produced through precision breeding technologies from regulatory requirements applicable in England for the environmental release and marketing of GMOs. It introduces two notification systems; one for precision bred organisms used for research purposes, and the other for marketing and other connected purposes.

## 3.10 USA

In response to advances in genetic engineering and new techniques including genome editing, the United States Department of Agriculture-Animal and Plant Health Inspection Service (USDA-APHIS) announced a new rule on May 18, 2020 that addresses the regulation of certain genetically engineered (GE) organisms, referred to as the "Sustainable, Ecological, Consistent, Uniform, Responsible, Efficient" (SECURE) Rule[68]. The Rule is the first comprehensive revision of the 7 CFR Part 340 regulations established in 1987 to govern the importation, interstate movement, and environmental release of GE organisms.

Under the new rule, products developed through genome editing are exempted from obligations under the regulation 7 CFR part 340 when i) changes in the plant product's genome are deletion(s) of any size; ii) the plant product's genome contains only targeted substitutions of a single base pair; or iii) the plant product's genome solely contains solely introductions from sequences derived from the plant's natural gene pool or edits from sequences which are known to correspond in the plants natural gene pool.

The exemptions are based on the following principles:

- Plants created through conventional breeding have a history of safe use related to plant pest risk;
- The types of plants that qualify for these exemptions can also be created through conventional breeding; and
- There is no evidence that use of recombinant deoxyribonucleic acid (DNA) or genome editing techniques necessarily and in and of itself introduces plant pest risk, irrespective of the technique employed.

Applicants may request confirmation that their products are exempted and APHIS will provide a written confirmation within 120 days. This replaces the previously offered voluntary consultation process "Am I regulated according to 7 CFR parts 340" (AIR).

On 25 May, 2023, US Environmental Protection Agency (EPA) announced that like USDA, it will exempt gene-edited plants from an in-depth review process if the change could have been achieved with conventional breeding[69]. To be effective from July 31, 2023, the Final Rule will exempt plant-incorporated protectants (PIPs) created through genetic engineering from a sexually compatible plant and "loss-of-function PIPs," from certain registration requirements under the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA), and from the requirements to establish a tolerance or tolerance exemption for residues of these substances on food or feed under the Federal Food, Drug, and Cosmetic Act (FFDCA). Un-

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[67] UK Parliament (2023) Genetic Technology (Precision Breeding) Act, 2023 https://bills.parliament.uk/bills/3167 (Accessed on July 25, 2023)

[68] USDA-APHIS (2020) Movement of certain genetically engineered organisms. Federal Register 85 FR 29790–29838. https://www.federalregister.gov/documents/2020/05/18/2020-10638/movement-of-certain-genetically-engineered-organisms. Accessed on July 25, 202340 whenc

[69] Environmental Protection Agency (2023) Pesticides: Exemptions of Certain Plant-Incorporated Protectants Derived from Newer Technologies. Federal Register 88(104): 34756 – 34779

like USDA, the agency will require companies to submit confirmatory safety data, such as evidence that the changes don't increase pesticide levels beyond those found in food from conventional crops.

## 3.11 Regulatory approaches notified in Asian region

In Asia, five countries viz. Japan, China, India, Philippines and Russia have issued their regulatory policies for genome edited plants as described below:

**i.** **China**: In January 24, 2022, the Ministry of Agriculture and Rural Affairs (MARA) of the People's Republic of China issued the "Guidelines for Safety Evaluation of Gene-Edited Plants for Agricultural Use (Trial Edition)" which for the first time establish application procedures and requirements for gene-edited plants that do not introduce exogenous genes[70]. Applications have been divided into four categories based on the risk profile of the target trait: 1) target traits that do not increase risk of environmental and food safety; 2) target traits that may increase environmental safety risk; 3) target traits that may increase food safety risk; 4) target traits that may increase environmental and food safety risk. Within each requirement category separate requirements are provided for product applications for production (cultivation) and applications for import (as materials for processing). The guidelines introduced a simplified procedure i.e., if the risk is found to be low, a safety certificate can be applied for commercial production after a small-scale test. Safety evaluation involves review of the plants details and data related to biosafety and food safety by the MARA.

On May 9, 2023 MARA updated the Trial Edition (Review Rules)[71]. The Review Rules which clarifies the classification criteria and requirements for evaluating gene-edited plants. The rules provide operational guidance in the areas of molecular function, environmental safety, and food safety, including acceptable data. These evaluations can all be carried out in the intermediate test stage.

**ii.** **India**: In India, new gene technologies are regulated under the Rules for the manufacture, use, import, export and storage of hazardous micro-organisms, GE organisms or cells, 1989 (Rules, 1989) notified under the Environment (Protection) Act, 1986.

On March 30, 2022, Ministry of Environment, Forest and Climate Change (MoEF&CC) exempted genome edited plants falling in the categories of SDN-1 and SDN-2 that are free from any transgenes from the provisions (Rules 7 to 11) of Rules, 1989[72], whereas products of SDN-3 (with transgenes) will be treated in the same way as GE organisms under Rules, 1989. The Office Memorandum indicates that the process of genome edited plants is to be carried out under containment, until free from exogenous introduced DNA and will be regulated by Institutional Biosafety Committee following stipulated guidelines under information to Review Committee on Genetic Manipulation. Once it is confirmed that gene edited plants are free from exogenous introduced DNA, their release as new variety, development and evaluation will be as per other applicable Laws/Acts/Rules.

The Department of Biotechnology (DBT) has issued "Guidelines for the Safety Assessment of Genome Edited Plants, 2022"[73] and "Standard Operating Procedures (SOPs) for Regulatory

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[70] USDA FAS GAIN Report (2021) MARA Issues First Ever Gene-Editing Guidelines. GAIN Report Number: CH2022-0015. https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=MARA%20Issues%20First%20Ever%20Gene-Editing%20Guidelines_Beijing_China%20-%20People%27s%20Republic%20of_01-26-2022.pdf. Accessed on July 25, 2023

[71] USDA FAS GAIN Report (2023). MARA Updates Rules for Review of Gene-Edited Plants for Agricultural Use. GAIN Report Number: CH2023-0080.
https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=MARA%20Updates%20Rules%20for%20Review%20of%20Gene-Edited%20Plants%20for%20Agricultural%20Use%20_Beijing_China%20-%20People%27s%20Republic%20of_CH2023-0080.pdf. Accessed on July 25, 2023

[72] Ministry of Environment, Forest and Climate Change (2022) Exemption of the Genome Edited plants falling under the categories of SDN-1 and SDN-2 from the provisions of the Rules, 1989. http://forest.delhigovt.nic.in/sites/default/files/Exemption%20of%20the%20Genome%20Edited%20plants%20falling%20under%20the%20categories%20of%20SDN-1%20and%20SDN-2%20from%20the%20provisions%20of%20the%20Rules%2C1989.pdf. Accessed on July 25, 2023

[73] Department of Biotechnology (2022) Guidelines for the Safety Assessment of Genome Edited Plants, 2022 https://dbtindia.gov.in/sites/default/files/Final_%2011052022_Annexure-I%2C%20Genome_Edited_Plants_2022_Hyperlink.pdf. Accessed on July 25, 2023 Accessed on July 25, 2023

Review of Genome Edited Plants under SDN-1 and SDN-2, 2022"[74] . These SOPs are targeted to meet the threshold for exemption i.e., the genome edited plant(s) must fall within SDN-1 and SDN-2 categories and must be free of exogenously introduced DNA.

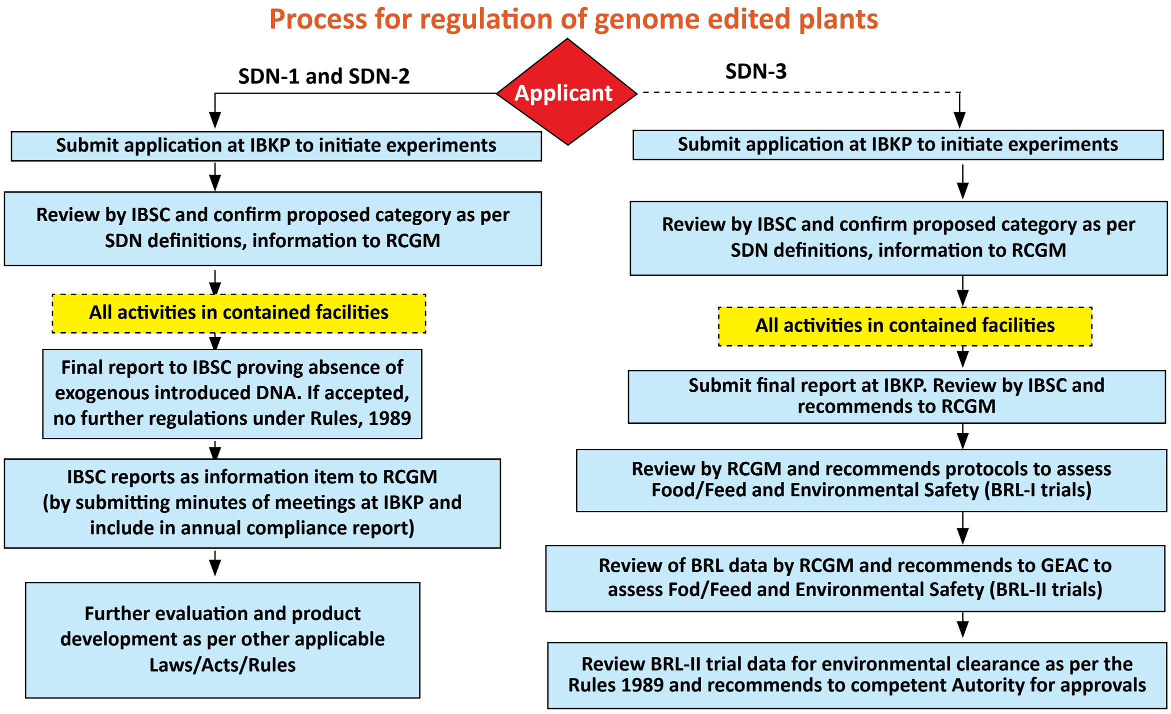

**Figure 15.** Process for regulation of genome-edited plants

*Source: https://ibkp.dbtindia.gov.in/Content/Rules*

iii. **Japan**: The policy for handling genome edited organisms in Japan was announced in 2019 by the Ministry of Environment (MoE) from the context of environmental safety and Ministry of Health, Labour & Welfare (MHLW) for food safety. The policy of both ministries states that genome edited organisms are exempted from the regulations of GMOs.[75]

The policy by MoE provides specific conditions under which the Cartagena Act will not be applicable to the genome edited organism [conditions under which the organism will not be considered as a Living Modified Organism (LMO)]. The organism transformed with extracellularly processed nucleic acids is regarded as an LMO, and regulated under the Cartagena Act, until it is confirmed that there are no remnants of inserted nucleic acids or its replicated products. If the finally obtained organism contains extracellularly processed nucleic acids and/or their replicates integrated into the host's genome, it will be considered to be an LMO.

The policy by MHLW indicated that foods derived from genome editing technology that contain transgenic genes and/or fragments of transgenic genes are considered similar to recombinant DNA technology and are required to undergo a safety review under the current standards and regulations. However, when there are no transgenic genes and/or fragments of transgenic genes in the final product such as genome edited foods will not be considered to be foods derived from recombinant DNA technology.

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[74] Department of Biotechnology (2022) Standard Operating Procedures (SOPs) for Regulatory Review of Genome Edited Plants under SDN-1 and SDN-2, 2022. https://dbtindia.gov.in/sites/default/files/SOPs%20on%20Genome%20Edited%20Plants_0.pdf. Accessed on July 25, 2023.

[75] Tachikawa, M. and M. Matsuo (2023) Divergence and convergence in international regulatory policies regarding genome-edited food: How to find a middle ground. Frontiers in Plant Science 14: 1105426.

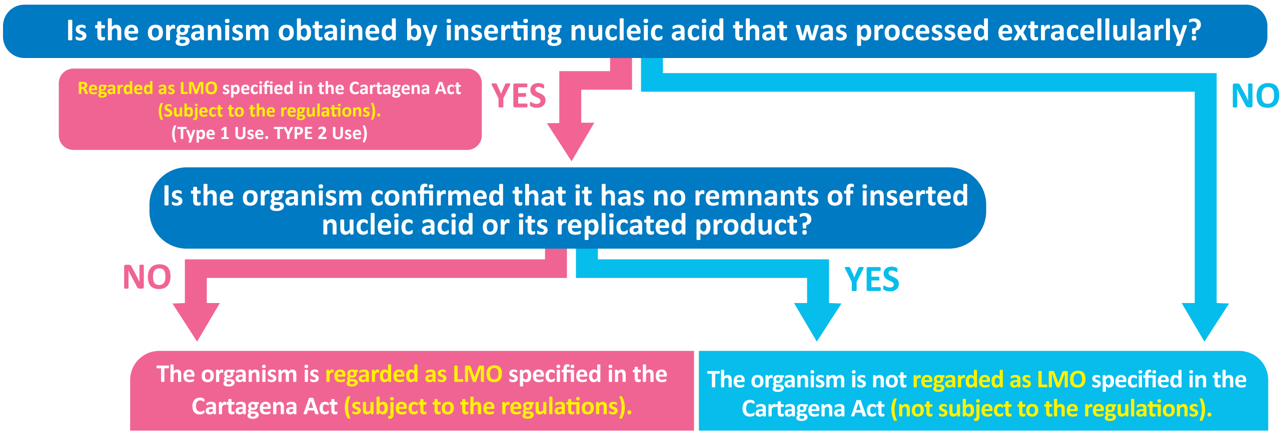

**Figure 16:** Flow chart issued by Japanese Environment Ministry

*Source: https://apps.fas.usda.gov/newgainapi/api/report/downloadreportbyfilename?filename=Environment%20Ministry%20Finalizes%20Policy%20for%20Regulating%20Genome%20Editing_Tokyo_Japan_3-6-2019.pdf Accessed on July 25, 2023*

**iv.** **Philippines**: The Philippine Department of Agriculture (DA) has published the rules and procedures for the evaluation of products of plant breeding innovations (PBI) vide Memorandum Circular No. 8, Series of 2022 (MC8), providing for the determination of whether or not the gene-edited plants are to be considered as genetically engineered[76].

The National Committee on Biosafety of the Philippines (NCBP) defines PBIs as a set of molecular genomics and cellular techniques for targeted and efficient development of new and improved crop varieties in a faster and more precise manner compared to conventional methods. Section 1 of MC8 states that products of PBI with a novel combination of genetic material derived from the use of modern biotechnology are considered genetically engineered and will have to follow the rules and regulations for such prior to release. Without the presence of a novel combination of genetic material, the PBI product will be considered a conventional product.

The developer must submit a request to the Director of the Bureau of Plant Industry for Technical Consultation for Evaluation and Determination for the PBI product to be evaluated as genetically engineered or conventional. If the product is declared as non-GE, a Certificate of Non-Coverage from the Joint Department Circular (JDC1), s2021 will be released to the developer and to the public for cultivation and consumption.

v. **Russia**: In 2019, a decree of the President of Russia (Resolution of 22 April 2019 no. 479) established funding for genome editing and classified transgene-free edited crops as equivalent to those generated by conventional breeding. Submitted by the Russian Ministry of Science and Higher Education pursuant to the Russian President's Executive Order No. 680 on Developing Genetic Technologies in the Russian Federation, the signed resolution approves a scientific-technical programme for the genetic technologies development for 2019-2027. The Programme is designed to facilitate the accelerated development of genetic technologies, including genetic editing; to establish scientific and technological groundwork for medicine, agriculture and industry. The Programme also aims to improve the system of preventing biological emergencies and monitoring in this area[77,78].

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[76] Department of Agriculture, Republic of the Philippines (2022) Rules and Procedure to Evaluate and Determine when Products pf Plant Breeding Innovations (PBIs). Memorandum Circular No. 8 https://www.da.gov.ph/wp-content/uploads/2022/06/mc08_s2022_Revised.pdf. Accessed on July 25, 2023

[77] Russian Ministry of Science and Higher Education (2019) Approval of the Federal Research Programme for Genetic Technologies Development for 2019–2027, http://government.ru/en/docs/36457/. Accessed on July 25, 2023

[78] Dobrovidova, O. (2019) Russia joins in global gene-editing bonanza. Nature 569:319-320

## 3.12 Asian countries with gene editing policy in pipeline

i. **Indonesia**: Indonesia has drafted a regulation on genome edited products in early 2021. According to the draft, genome edited products will be regulated as GMOs when they contain a novel combination of DNA ("from outside the taxon") or if foreign DNA is present in the final product. If this is not the case the products will be deregulated. Further details are awaited[79].

ii. **South Korea**: South Korea is in the process of revising its existing "Living Modified Organism (LMO) Act" to cover products of innovative biotechnologies, including genome edited products. Discussions have been underway for introduction of a preliminary review system for low-risk LMOs, covering "LMOs created through modern biotechnology" under Article 2 (Definition) of the LMO Act.

    As an initiative of the Ministry of Trade, Industry and Energy (MOTIE), a partial amendment bill to the Transboundary Movement, etc. of LMO Act has been submitted to the National Assembly in July 2022 to allow the request for exemption from risk assessment if the novel LMO using new technologies such as genome editing techniques are confirmed to be safe at a level similar to natural mutation or traditional breeding through the preliminary review system[80]. It has been stated that if the novel LMO does not contain foreign genes during its development process, or if any foreign genes introduced during development are not present in the final product and are at a level similar to traditional breeding or natural mutation, it could be exempted from risk assessment by the competent national authority.

iii. **Taiwan**: In Taiwan, the regulatory policy on GE products is being reviewed by an ad-hoc expert committee by the Taiwan Food and Drug Administration. Currently, mandatory pre-consultation and notification is required for GE foods and basic/safety information (i.e., evidence of no foreign DNA, or adverse effects) and reference materials need to be submitted for review, based on the draft policy disclosed in 2021. The cultivation of genome-edited products in Taiwan will be controlled under the Plant Variety and Plant Seed Act administered by the Council of Agriculture. The definition of whether genome-edited products are captured under this regulation is not clear, and any new policy will need to clarify whether there will be exemptions for any genome-edited products[81].

iv. **Thailand**: The National Center for Genetic Engineering and Biotechnology (BIOTEC), Ministry of Higher Education, Science, Research and Innovation (MHESI) has prepared guidelines, wherein food products derived from genome editing are proposed to be assessed based on three categories: Category I (SDN-1) with minimal data requirements; Category II (SDN-2) with case-by-case additional requirements to assess product characteristics; and Category III (SDN-3) with more requirements including compositional, toxicological, and allergenic data, among others[82].

v. **Vietnam**: In 2019, there were discussion on plant breeding innovations (PBIs) by way of scientific outreach for public awareness and three workshops have been conducted. There are no draft guidelines published as yet, but Vietnam Academy of Agricultural Sciences (VAAS) have initiated discussions on ongoing R&D developments, local capacities, and global and regional policy developments for PBIs.

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[79] Prasetya, B. and S. Nugroho (2021) The Role of Genome Editing to Boost Bioeconomy Significantly: Opportunities and Challenges in Indonesia. Proceedings of The 5th SATREPS Conference, Bogor 3(1): 47-62

[80] USDA FAS GAIN Report (2022) Agricultural Biotechnology Annual. GAIN Report Number: KS2022-0024. https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=Agricultural%20Biotechnology%20Annual_Seoul_Korea%20-%20Republic%20of_KS2022-0024.pdf. Accessed on July 25, 2023

[81] Jones, M. G., J. Fosu-Nyarko, S. Iqbal, M. Adeel, R. Romero-Aldemita, M. Arujanan, M., M. Kasai, X. Wei, B. Prasetya, S. Nugroho, O. Mewett, S. Mansoor, M. J. A. Awan, R. L. Ordonio, S. R. Rao, A. Poddar, P. Hundleby, N. Iamsupasit and K. Khoo (2022) Enabling trade in gene-edited produce in Asia and Australasia: The developing regulatory landscape and future perspectives. Plants 11(19): 2538.

[82] USDA FAS GAIN Report (2022). Agricultural Biotechnology Annual. GAIN Report Number: TH2022-0071. https://apps.fas.usda.gov/newgainapi/api/Report/DownloadReportByFileName?fileName=Agricultural%20Biotechnology%20Annual_Bangkok_Thailand_TH2022-0071.pdf. Accessed on July 25, 2023

vi. **Singapore**: In Singapore, draft policy (Regulatory Approach for Food Derived from Genome Edited Crops) developed by the Singapore Food Agency (SFA) has proposed a "risk- based product trigger approach for foods derived from genome edited crops". It has been indicated that genome edited crops that do not contain foreign DNA do not require pre-market safety assessment, and are to be registered with SFA accompanied by safety attestation of the crop. The genome edited crops that contain foreign DNA require pre-market safety assessment by the Singapore Genetic Modification Advisory Committee (GMAC) and final approval by SFA.

vii. **Pakistan**: The National Institute for Biotechnology and Genetic Engineering (NIBGE) has initiated discussions regarding regulation of genome edited products in Pakistan. The discussions so far indicated that SDN-1 and SDN-2 products will not be regulated as GMOs, whereas when a foreign gene is present, the product will be treated as a GMO (SDN-3). The Institutional Biosafety Committee (IBC) considers all genome-edited cases and submits recommendations on the status of projects or research outcomes to the National Biosafety Committee (NBC)[83].

viii. **Bangladesh**: Bangladesh Academy of Sciences (BAS) initiated the discussion on procedure for genome edited plants in Bangladesh. Bangladesh Agricultural Research Council (BARC) organized a workshop to discuss SOPs for gene edited plants in Bangladesh. The process is under discussion.

## 3.13 Discussion at international fora

*Cartagena Protocol on Biosafety*

The Cartagena Protocol on Biosafety (CPB) to the Convention on Biological Diversity (CBD) is an international treaty governing the transboundary movements of Living Modified Organisms (LMOs) resulting from modern biotechnology. It was adopted in 2000 and entered into force in 2003. As on date, there are 173 Parties to the Protocol.

The CPB contains provisions to establish rules and procedures that are applicable to the transboundary movement of specific categories of LMOs, including the risk assessment of its potential adverse effects on the conservation and sustainable use of biodiversity.

Two definitions in particular under the Protocol are relevant for regulators on establishing if this treaty and related domestic legislations apply to gene-edited organisms:

i. Living Modified Organism is any living organism that possesses a novel combination of genetic material obtained by modern biotechnology.

ii. Modern biotechnology means the application of a) *In vitro* nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells, or b) Fusion of cells beyond the taxonomic family that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

Periodic meetings are held by Parties to the CPB to review the implementation of the Protocol and make decisions necessary to promote its effective operations. The parties meet every two years, as part of the activities of the Convention on Biological Diversity (CBD) to negotiate implementation aspects of the treaties. Gene-editing has come up in the discussions under the Cartagena Protocol as a potential 'issue' requiring further risk assessment guidance, but Parties had different views and thus there was no agreement so far.

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[83] Jones, M. G., J. Fosu-Nyarko, S. Iqbal, M. Adeel, R. Romero-Aldemita, M. Arujanan, M., M. Kasai, X. Wei, B. Prasetya, S. Nugroho, O. Mewett, S. Mansoor, M. J. A. Awan, R. L. Ordonio, S. R. Rao, A. Poddar, P. Hundleby, N. Iamsupasit and K. Khoo (2022) Enabling trade in gene-edited produce in Asia and Australasia: The developing regulatory landscape and future perspectives. Plants 11(19): 2538.

Meanwhile, many countries that regulate LMOs, as defined in the Protocol, have determined that SDN-1 and SDN-2 types of genome editing do not result in the creation of a "novel combination of genetic material" and are not LMOs. SDN-3 genome editing involves targeted insertion and thus is to be regulated similar to LMOs.

*The Organisation for Economic Co-operation and Development*

The Organisation for Economic Co-operation and Development (OECD) and its member countries have been addressing issues related to biotechnology since 1982. The Working Party on Harmonisation in Biotechnology deals with environmental issues and the Working Party for the Safety of Novel Foods and Feeds focus on food safety issues. Their guidance documents usually provide complementary and more detailed content on biosafety issues. The OECD organized a conference on ''Genome Editing: Applications in Agriculture—Implications for Health, Environment and Regulation' in 2018 and published a meeting report in 2019. Proceedings of this workshop constitute a valuable source of information for regulators. Additionally, the OECD regularly publishes regulatory updates at the country level, compiling reports by its member countries.

## 3.14 Conclusions

It is evident from the above that there is a growing consensus that gene edited plants that do not contain exogenous foreign DNA should not be regulated under the same rules that apply to genetically engineered or transgenic plants. Most countries are moving towards regulation of SDN-1/SDN-2 genome edited products in the same way as products of conventional breeding, SDN-3 products are being treated in the same way as GMOs.

At present, more than 50% of the world's population live in countries with positive or partial positive decisions on exempting SDN-1 and SDN-2 gene edited plants from the GMO regulatory pathway. There appears a growing consensus that at least with gene edited crops, the regulatory approach should be product-based, rather than process-based.

# CHAPTER 4
# GENOME EDITED PLANTS IN THE MARKET

## 4.1 Introduction

The agricultural sector plays pivotal role in supplying food, fiber, and essential resources to the world. Crops get cultivated in different parts of the world based on varying agroclimatic conditions, efficiency of production and cost of production. Many of these crops are traded internationally, in both raw and processed forms, depending on consumer markets. These crops are critical for the food and nutritional security and thus the trade policies for agricultural commodities across the world are extremely important, especially for low and lower-middle income countries in the Asian region.  The international trade of sowing seeds – especially those of staple field and vegetable crops - has also logged substantial growth in the past decade, During the six-year period starting 2009 and ending 2015, the volume of seeds traded globally grew by almost 80%, while the value of seed exports increased by 37% during the same period[84]. This accounts for about one-fifth (20 per cent) of the total global seed market in value. The cumulative share of vegetable seeds in trade of seeds by Asia-Pacific countries is even greater, in 2019 accounting for about half the value of all seed consignments in the region[85].

Major crops like cereals, pulses, oilseeds, fruits and vegetables are being gene edited to be more resilient, resistant and/or tolerant to climate change, biotic and abiotic stresses, require less chemical inputs in cultivation and offer improved production and incomes for farmers. Such genome edited crops are expected to play a pivotal role in addressing global food and seed supply chain challenges. It is important to ensure that policies and capacities are in place in the Asian region for smooth trade of genome edited crop varieties.

## 4.2 Regulations for development and trade of crops

Agriculture is a highly regulated sector in most economies, and it is important to recognize that there is no such thing as an unregulated agricultural activity. The regulation of crop improvement is governed by a combination of national and international guidelines and regulations. Although, specific frameworks and processes may differ among countries, their overarching purpose is to ensure the safety and quality of improved crop varieties.  Various regulations and standards are in place to ensure the safety, quality, and sustainability of agricultural inputs and practices.

Conventional agri-food regulatory systems involve registration and specific tests for testing new varieties in many countries. These tests ensure the distinctness, uniformity, stability (DUS), and safety of new varieties, while also considering their value for cultivation and use (VCU) with better yield contributing trait(s) over the existing or prevalent crop varieties. Farming practices are subject to regulations governing the use of fertilizers, pesticides, and herbicides. These regulations aim to minimize the environmental impact of agricultural activities and ensure the safety of agricultural products. In many cases, industry production codes and standards, such as organic requirements, further govern specific types of agricultural production and promote sustainable farming practices.

Trade and usage of grain are regulated through maximum residue limits for pesticide residues and quality and grading standards. These regulations ensure that grains meet quality standards and do not pose risks

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[84] OECD (2018) Concentration in Seed Markets: Potential Effects and Policy Responses. OECD Publishing, Paris

[85] APSA (2020) Asian Seed & Planting Material. Asian Seed 26(2):12
https://apsaseed.org/AsianSeed2020/Asian_Seed_MagQ2_2020_Apr_Jun.pdf. Accessed on July 25, 2023

to consumers. The use of grain in livestock feed is also regulated to ensure its safety for animal consumption, contributing to the overall safety and integrity of the food supply chain.

Various international standard setting bodies also contribute to quality management of agriculture processes by developing standards and other measures. Some play a crucial role in harmonizing regulations and facilitating trade. Some of the key international standards regulating agriculture and the foods trade include:

(a) **Sanitary and phytosanitary Measures (SPS) under World Trade Organization (WTO):** The WTO provides a framework for global trade rules, including agricultural trade. The SPS agreement allows WTO members to set their own standards on food safety and animal and plant health. However, these standards must be based on science, applied only to the extent necessary to protect human, animal or plant life or health, and not arbitrarily implemented to unjustifiably discriminate between countries where identical or similar conditions prevail.[86]

(b) **Codex Alimentarius Commission (CAC)**: The CAC, jointly established by the Food and Agriculture Organization (FAO) and the World Health Organization (WHO), develops international food standards, guidelines, and codes of practice. It covers food safety, food additives, pesticide residues, contaminants, etc. Codex standards are widely recognized and applied by many countries to ensure safe and quality food products. These standards, guidelines and codes of practice contribute to the safety, quality and fairness of this international food trade.[87]

(c) **International Plant Protection Convention (IPPC)**: The IPPC, under the auspices of the FAO, sets international standards for plant health to prevent the spread and introduction of pests and diseases. It provides guidelines for phytosanitary measures, quarantine requirements, pest risk analysis, and the establishment of pest-free areas. Compliance with IPPC standards helps to protect agricultural crops, maintain biosecurity, and facilitate international plant trade[88].

(d) **The Organization for Economic Cooperation and Development (OECD)**: The OECD Committee for Agriculture (COAG) oversees OECD work on agriculture and food policy. It provides the evidence base and analysis to support governments in improving policy performance and creating an enabling environment for the sector to thrive.[89]

(e) **International Seed Testing Association (ISTA)**: ISTA works in developing standard seed testing methods, facilitates the trade of quality seeds and makes a valuable contribution to food security[90].

By adhering to these national and international regulations, the global plant breeding community, both public and private, has safely brought to the market thousands of new, improved plant varieties over the last several decades.

## 4.3 Global seed trade

Seed is the basic and most critical input for sustainable agriculture. The response of all other inputs depends on quality of seeds to a large extent. It is estimated that the direct contribution of quality seed alone to the total production is about 15 – 20% depending upon the crop and it can be further raised up to 45% with efficient management of other inputs. Seed movement is also very predominant across continents and countries. Access and affordability of quality seed is very important for agriculture and small farmers to survive in most countries.

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[86] World Trade Organization (WTO) Sanitary and phytosanitary measures. https://www.wto.org/english/tratop_e/sps_e/sps_e.htm. Accessed on July 25, 2023

[87] Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) About Codex Alimentarius. https://www.fao.org/fao-who-codexalimentarius/about-codex/en/. Accessed on July 25, 2023

[88] FAO and International Plant Protection Convention (IPPC) Overview. https://www.ippc.int/en/about/overview/. Accessed on July 25, 2023

[89] Organisation for Economic Co-operation and Development (OECD) About the Trade and Agriculture Directorate

. https://www.oecd.org/agriculture/about/#:~:text=The%20OECD%20Committee%20for%20Agriculture%20(COAG)%20was%20also%20established%20in,for%20the%20sector%20to%20thrive. Accessed on July 25, 2023

[90] International Seed Testing Association (ISTA) About us. https://www.seedtest.org/en/informations-footer/about-us.html. Accessed on July 25, 2023

Similarly, quality seeds of staple, horticultural and ornamental crops typically are moved across continents, through several countries before reaching end-users. Seeds are produced in one country based on a number of factors, including the efficiency of production systems, cost of production, suitability of climate, the level of Intellectual Property Rights protection, and counter-season production requirements. Seeds are then transported to different countries for further R&D, breeding, processing and/or testing requirements, before moving on to their final destinations, where they will eventually be distributed and sown by farmers and cooperatives. This system has enabled the overall seed supply system to be cost and quality efficient, which benefits farmers in all countries.

**Table 2: Export of seeds according to seed trade statistics by International Seed Federation in 2018** [91]

| | Quantity (metric tonnes) | Value (Billion USD) |
|---|---|---|
| **Field crops** | 3,892,182 (60 % of total volume) | $7.94 bn (61% of total value) |
| **Vegetable crops** | 142,505 (2.5% of total volume) | $4.58 bn (33% of total value) |

**Table 3: Import of seeds according to seed trade statistics by International Seed Federation in 2018** [92]

| | Quantity (metric tonnes) | Value (Billion USD) |
|---|---|---|
| **Field crops** | 4,088,014 (72 % of total volume) | $7.38 bn (57% of total value) |
| **Vegetable crops** | 130,112 (2.3% of total volume) | $4.53 bn (35% of total value) |

The entire seed market includes seeds produced and utilized domestically, and those traded internationally (about 20% of the total). Whether or not supply can keep up with demand in the coming years will depend on a number of factors that affect international seed movements. Following are highlights of recent and current international seed trade trends, globally, and regionally.

According to seed trade statistics compiled by the International Seed Federation, in 2018, 5.68 million tonnes of seed worth $13.8 billion were exported globally. This is compared to 5.63 million tonnes of seeds imported, worth $13.02bn, respectively.

## 4.4 Impact of plant breeding on the seed and food supply chains

Using quality seed is one factor that growers have control in optimizing or maximizing output. Quality seed means professionally produced seeds that meet a high standard of purity, and which have predictable performance. This performance can be quantified in terms of germination, disease resistance, and certain agronomic characteristics. The quality of seeds directly corelates with the resources and capabilities of the community of public and private plant breeders, seed companies, and distributors.

Regardless of the crop plant or breeding methods used, the life cycle of seed product development through to commercial release, even for plants with short generation times, is measured in years. Because of the long lead time, product development begins with predicting, many years in advance, the characteristics of the plant that would be important to farmers and consumers. The plant breeding team then set to work, mining, characterizing, and combining the genetic diversity of the plant into one final product that meets the criteria set by the plant breeder. In the breeding process, many thousands of plants are tested, cross-bred, retested to narrow down to a handful of plants for further development. In concert with the plant breeding team, the seed production would test and develop the conditions and practices supporting predictable and consistent production of seeds in commercial quantities that meet commercial specifications. At each step of plant breeding and seed production, there are standard performance measures and quality controls. New plant varieties are evaluated in multiple production areas over many growing seasons before introduction into commercial agricultural practice. Test trials are conducted in as few as 10 to 20 sites per year for some plants, to 75 to 100 sites per year for others. The trials can take from 5 to 10 years to complete. The process of plant breeding is a continuous iterative endeavour,

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[91] International Seed Federation. (2018) Global Seed Exports Accessed on July 25, 2023. https://worldseed.org/wp-content/uploads/2020/10/Export_2018.pdf

[92] International Seed Federation. (2018) Global Seed Imports Accessed on July 25, 2023. https://worldseed.org/wp-content/uploads/2020/10/Import_2018.pdf

frequently needing adjustment to address changing market demands, evolving pest and disease pressures, and changing growing environments.

It is in the context of plant breeding and seed production as a whole, as well as the growing understanding of genetics and plant biology, that genomic enabled tools, such as genome editing can be deployed to enhance the efficiency and effectiveness of plant breeding.

Predictable seed movements across borders (i.e. reliable and transparent logistics and phytosanitary clearance) is an important aspect of providing quality seed to the market place.  Additionally, counter seasonal product of commercial seed is a standard practice, and re-export of seed is common.  Therefore.  the seed industry is dependent on consistent, science-based policies, not only for products of genome editing, but also for phytosanitary requirements, and intellectual property protections.

## 4.5 Impact of gene editing on agriculture trade

Continual innovation in plant breeding is crucial for both the seed industry and the sustainability of the global agricultural and food system, particularly at a time of rapid growth in the global population and the challenges of climate change. A key factor that incentivizes and protects the continuation of seed innovation is a transparent, consistent regulatory approach that is risk proportionate, based on the best available scientific evidence, and minimizes unnecessary barriers to seed movement.

With the advent of plant breeding innovations such as genome editing, policy makers and regulatory authorities appreciated that in many cases, the final outcome of genome editing.  may produce plants that would not conform with the definition of an LMO in the Cartagena Protocol on Biosafety.  As such, these products of new breeding technologies will be outside the purview of the Protocol.   As early as 2010, regulatory authorities around the world began to consider clarification of their GMO regulations with regards to products of plant breeding innovation such as genome editing.

Many countries recognize the importance of harmonized, compatible regulatory approaches to products of genome editing. In 2018, at the World Trade Organization (WTO) Sanitary and Phytosanitary Committee meeting, a group of countries introduced the International Statement on Agricultural Applications of Precision Biotechnology, which is now supported by 11 members of the WTO.[93] The text of the international statement is non-binding on supporting countries, but calls for coordination of science-based, internationally harmonized regulatory approaches to  prevent asymmetries,  and minimize unnecessary barriers to seed movement and potential trade disruption. The statement further acknowledges the importance of small and medium enterprises and public sector research in bringing innovation to market, of risk proportionate regulatory approaches that minimize trade barriers, of avoiding arbitrary distinction between like products because of production methods, and of collective dialogue among trading partners.

It is evident that risk proportionate, based on the best available scientific evidence for genome edited shall minimize unnecessary barriers to seed movement[94].

## 4.6 Need for harmonization

The genome editing technology is continuously evolving with discovery of superior quality enzymes and gene editing systems. Countries must exert effort to ensure that policy and regulations are apace with developments in plant breeding technologies. Globally, regulatory bodies and governments are currently at different stages in formulating  policy and guidelines for gene-edited products.

With the increase in the demand for food, there is a need to harmonize regulation of gene edited crops and their products. Harmonization of regulations is crucial to the increase in investments necessary to harness

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[93] WTO (2018) International Statement on Agricultural Applications of Precision Biotechnology. Doc. No. 18-6871 https://docs.wto.org/dol2fe/Pages/FE_Search/FE_S_S009-DP.aspx?language=E&CatalogueIdList=249321 Accessed on July 25, 2023

[94] Jenkins D., R. Dobert, A. Atanassova and C. Pavely (2021) Impacts of the regulatory environment for gene editing on delivering beneficial products. In Vitro Cellular & Developmental Biology-Plant 57(4): 609-626.

this technology. To meet a growing demand for new plant varieties, and be able to evaluate them more efficiently, the international movement of germplasm and other genetic resources required for gene-editing research has to be facilitated through a regionally and globally harmonized regulatory regime.

## 4.7 Conclusions

Discrepancies in gene editing regulations across nations and geographies would make it more difficult not only for agri-food companies to trade their products globally, but also to comply with varied laws. Nations having complex regulation will stand to lose out on revenue. Practical difficulties in detection and supervision of products across trading countries will slow down the innovation, investment and adoption of novel technologies in plant breeding.

Transparent, science-based, policies, rules and regulations would facilitate adoption of the technology by both the public and private sectors, and thereby improve crop diversity and selection for breeders and farmers. On the other hand, an unreasonably stringent regulatory system would inhibit growth of and access to the technology, the adoption for which would be cost prohibitive.

# CHAPTER 5

# WAY FORWARD

Gene editing is a precise breeding tool that enable breeders to produce novel traits by introducing specific, non-random changes to the genome. This tool adds speed, precision and efficiency to plant breeding programs. Notwithstanding its tremendous potential from crop improvement, regulatory policies for gene editing will greatly affect its widespread application and adoption, both by public and private institutions.

Consistent application of international standards is crucial to the efficient operation of the global agri-food production system. If gene edited crops are to make significant contributions to global food and nutrition security, enabling regulatory policies and consistent standards must be put in place by trading partners. This may be done with minimum cost if plant varieties developed by methods like gene editing are regulated like varieties developed by conventional breeding. The gene editing market is on the brink of remarkable growth attributed to the escalating government funding and proliferation of genomics projects, which are poised to significantly impact the market. In the US National Institutes of Health (NIH) expanded funding with a USD 89 million allocation for new projects. Simultaneously, the European Union initiated the Horizon 2020 program, a significant financial resource dedicated to advancing genomics research and gene editing ventures. Additionally, global players like China, Japan, and South Korea have established robust national genomics programs, fueling the advancement of gene editing technologies. Thus it is observed that some of the countries in Asia-Pacific region have already developed/articulated national guidelines/policies that deal with research on gene edited organisms and their possible products, while other countries are in the process of formalizing their regulatory policies . Given the lower cost and more basic infrastructure requirements for gene editing, it may facilitate the improvement of niche crops with small acreage, and as such may benefit the small holder farmers in these nations. This technology can likewise be employed to introduce traits that may address climate change and socio-economic conditions specific to the region.

APAARI, under its Program on APCoAB, took several initiatives to hold expert consultations at regional level and series of webinars at the global level. Engaging global experts in gene editing and concerned stakeholders (researchers, research managers, policy makers from government ministries, and industry representatives), participants deliberated on policy issues related to the regulation of gene editing research and development of gene-edited products. Participants recognized that gene edited varieties can potentially contribute to food and nutritional security as well as to the protection of the environment. Based on the extensive discussions with experts and other stakeholders the following four areas of strategic policy recommendations are made to maximize the potential of gene editing in food and nutrition security in Asia-Pacific region:

**A. Meeting the Challenges of the Enabling Environment**

1. An enabling environment for gene editing is extremely important. Individuals and organizations adapt the innovations, related policies, and supporting investments through demand-driven and bottom-up approaches. An enabling environment includes national institutional set-up, its implicit and explicit rules, its power structures and the policy and legal environment, in which individuals and organizations function and develop respective competencies and capabilities. Therefore, science-based, predictable and proportionate regulations with clear timelines are urgently required to encourage innovations meeting ethical, safety, economic and technical concerns associated with gene editing. Countries should clarify the scope of their regulation for the products of gene editing at the earliest, and revisit their regulatory mechanisms and policies to allow greater use of gene editing technology.

2. Policy approaches should not hamper agricultural innovations that can benefit farmers and the society at large. Developments in countries in the Asia-Pacific region (Australia, India, Philippines and Japan) exclude certain categories (SDN-1 and SDN-2) of gene editing products from the scope of GM regulation: Australia has expressly excluded all applications of

SDN-1; and Japan has excluded SDN-1 on the basis that it does not involve the use of “extracellularly processed nucleic acids”. These exclusions are based on the appreciation of naturally occurring cellular repair mechanism of nonhomologous end joining. Similarly, several countries of Africa and Latin America have adopted approaches more aligned with the criteria listed above, and products developed using oligonucleotide-directed mutagenesis (ODM), SDN-1 and SDN-2 have been exempted from GM regulatory requirements. Among the different gene edited varieties, only those developed using SDN-3, or those that contain DNA from sexually incompatible species, should be subjected to GM safety assessment on a case-by-case basis.

3. Ambiguity in regulatory requirements causes unpredictable delays in approvals, thereby increasing costs, deterring innovation and restricting sometimes even blocking product pipelines. These costs also effectively eliminated small- and medium-sized enterprises (SMEs) from being able to compete in the crop innovation front. Science-based, predictable and proportionate regulations with clear timelines are urgently required to encourage innovations. It is recommended that countries should clarify the scope of their regulation for the products of gene editing at the earliest.

4. Should it be determined that a sub-set of gene-edited plants may warrant regulation as GM, then harmonization of approaches within the Asia-Pacific region is important for collaboration in research, capacity development, regulation and trade. Efforts towards finding the common ground should be facilitated by organizing interactive meetings among the researchers and the regulatory agencies in the region and should also be informed through appropriate stakeholder engagement and/or consultations.

5. Sharing of policy insights and scientific advice among trading partners, and within the region, should be encouraged. Such may hasten the evolution of an enabling harmonized regulatory approach for gene editing research and hasten product development. Sharing may take the form of dissemination of policy briefs, product development updates, exchange of information among regulatory agencies and periodic strategic communication among stakeholders.

**B. Enhancing Communications and Information Exchange:**

6. Significant efforts are needed from all stakeholders to improve and prioritize communication and information exchange about gene editing, particularly focusing on how gene editing may be considered as an extension of conventional plant breeding. Focused programs for communicating science-based information in easy-to-understand language should be initiated by academics, industry and science communication experts from both public and private sectors. Enhanced investments are required in (i) developing technical and functional capacities (soft skills) of scientists, prospective researchers, policymakers, and young biotech entrepreneurs to adopt more strategic processes and policy intervention to navigate complexities for better engagement in learning, collaboration, and partnerships activities; (ii) knowledge management (KM) and communication to better promote gene editing technology by addressing political and social concerns, and long-term benefits through enhanced information, education and communication (IEC).

**C. Encouraging Public-Private Partnerships:**

7. Public-Private partnership (PPP) is vital for successful transformation to a new economy through use of innovations and technologies in agriculture. While public sector funding is essential, the role of private sector in investing in gene editing research and product development is equally important. Public sector investment provides skilled manpower and the knowledge base for innovation but partnerships are essential for product development and adoption. Public-public, public-private and private-private should be encouraged: better mechanisms for sharing knowledge, technology and resources need to be in place to enable such partnerships. A global or regional consortium of private sectors with a more innovative funding system may trigger regular investment in gene editing research. Capacity and competency building in research and development, deployment and delivery and eventual marketing of products of gene editing should be enhanced at the regional level.

8. Partners need to provide clarity on the sharing of

intellectual property (IP), commitment to funding, sharing of infrastructure, resources (e.g., public sector to provide field infrastructure, private sector to provide laboratory resources), ownership of regulatory data, stewardship, and use of the technology in their complementary and collaborative programmes.

**D. Building Institutional Capacity**

9. Crops as well as areas of improvement need to be prioritized for an efficient deployment of gene editing technology and their products. The first applications of gene editing in the country can set precedents, and hence proactively establish effective policies. The innovative institutional arrangements, networks and collaboration will contribute substantially to development of the human capital needed to ensure the judicious application of these advanced tools and technologies in the region. Similarly, the regional collaborations and networks can also contribute to capacity building, communication strategies, policy development and risk-benefit communication.

To sum up, the speed of new scientific developments in genome editing has outpaced international and regional policies and regulations. Asia-Pacific countries are at different levels in scientific and regulatory side. A High Level Policy Dialogue of the countries in the region would be very useful for assessing the status of institutional and regulatory capacities and the way forward specially for the developing the least developed countries.

# Annexure-1

# Composition of Steering Committee
## for preparation of Resource Document on Gene Editing for Sustainable Agriculture and Food Security in Asia-Pacific Region

**Chair** – Dr. Ravi K. Khetarpal, Executive Secretary, APAARI (ravi.khetarpal@apaari.org)

**Members** –

1. Dr. Norwati Adnan, Director, Research & Evaluation Section, Department of Biosafety, Malaysia (norwati@biosafety.gov.my)
2. Dr. Flerida Carino, Retired Professor of Chemistry, University of the Philippines Diliman and Member, Biosafety Committee, Department of Science & Technology, Philippines (facarino@gmail.com)
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4. Dr. Ho-Min Jang, Korea BCH Focal Point, Korea Biosafety Clearing House (hmjang@kribb.re.kr)
5. Dr. Morven A McLean, Former CEO, Agriculture and Food Systems Institute. [Currently: Bill & Melinda Gates Agricultural Innovations]
6. Dr. Heidi Mitchell, Office of the Gene Technology Regulator, Australian Government Department of Health, MDP 54, GPO Box 9848, Canberra, ACT, 2601, Australia (Heidi.Mitchell@health.gov.au)
7. Dr. Ryo Ohsawa, School of Life and Environmental Sciences, University of Tsukuba, Japan (osawa.ryo.gt@u.tsukuba.ac.jp)/ Dr. Manabu Takahara, National Agriculture and Food Research Organization (mtakah@affrc.go.jp)
8. Dr Roland Schafleitner, Head-Molecular Genetics, Flagship Program Leader – Vegetable Diversity and Improvement, World Vegetable Centre, Tainan, Taiwan (roland.schafleitner@worldveg.org)
9. Late Dr Kiran K. Sharma, Retired Deputy Director General, International Crops Research Institute for the Semi-Arid Tropics (ICRISAT), India

**Co-conveners**

1. Dr. Vibha Ahuja, Chief General Manager, Biotech Consortium India Limited, India (vibhaahuja@biotech.co.in)
2. Dr. Rishi Tyagi, Former Coordinator, Asia-Pacific Consortium on Agricultural Biotechnology and Bioresources (APCoAB), APAARI, Thailand

# Annexure-2

## Webinar Series on
## "Applications of Gene Editing in Sustainable Agriculture and Food Security in Asia-Pacific Region"

Asia-Pacific Association of Agricultural Research Institutions (APAARI), in collaboration with Korea Biosafety Clearing House (KBCH) and Biotech Consortium India Limited (BCIL) organized a series of three webinars on topics related to "Applications of gene editing in sustainable agriculture and food security in Asia-Pacific region" to solicit inputs from key stakeholder groups. The webinar series was also aimed towards spreading awareness among various stakeholders about gene editing techniques, recent advancements in Asia-Pacific region, differential status of regulations and intellectual property rights landscape with respect to gene editing applications.

*Webinar 1: Genome editing tools and its applications for targeted plant breeding, July 21, 2021*
*Webinar 2: Advancing genome edited plants from lab to land, August 4, 2021*
*Webinar 3: Enabling policies for genome editing in agriculture, August 18, 2021*

More than 2500 participants from 60 countries registered for the events and on an average about 700 participated in each of the webinar.

CHAIRPERSON

WEBINAR SERIES

Applications of Gene Editing in Sustainable Agriculture and Food Security in Asia-Pacific Region

WEBINAR
1
Genome editing tools and its applications for targeted plant breeding

Date: July 21, 2021
10.30 AM to 12.30 PM
ICT (Bangkok time)

Registration

**Prof. Ryo Ohsawa**
Dean, Faculty of
Life and Environmental Sciences,
University of Tsukuba, Japan
Committee member of ERA under the Japanese
Ministry of Environment and the
Ministry of Agriculture, Forestry and Fisheries
President, Japanese Society of Breeding

PRESENTERS

**Dr. Hiroshi Ezura**
Professor, Fundamental Genetic Engineering and
Molecular Breeding Technologies University of Tsukuba, Japan

**Dr. Jose (Jimmy) Botella**
Professor of Plant School of Agriculture and Food Sciences,
University of Queensland, Australia

PANELLISTS

**Dr. Zeba Islam Seraj**
Professor, Department of Biochemistry and
Molecular Biology, University Dhaka.
Director, cBLAST DU (Center for Bioinformatics
Learning and Advanced Systematics Training,
University of Dhaka), President GNOBB,
Global Network of Bangladeshi Biotechnologists

**Dr. T. R. Sharma**
Deputy Director General
(Crop Science)
Indian Council of Agricultural
Research, India

**Dr. Donghern Kim**
Vice President
Future Food Resources Forum
Korea

**Dr. Chwan-Yang HONG**
Professor, Department of
Agricultural Chemistry
National Taiwan University,
Taiwan

**Prof. Kok Gan Chan**
Deputy Head of Department,
Institute of Biological Sciences,
Faculty of Science,
University of Malaya,
Kuala Lumpur, Malaysia

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## WEBINAR SERIES

## Applications of Gene Editing in Sustainable Agriculture and Food Security in Asia-Pacific Region

### WEBINAR 2

### Advancing Genome Edited Plants from Lab to Land

Date:
August 4, 2021, 10.30 AM – 12.30 PM
ICT (Bangkok time)

Registration
https://zoom.us/meeting/register/tJAqdumsqDooGNApndwbg1Zl6ldtYcsrLM5y

**CHAIRPERSONS**

**Dr. Heidi Mitchell**
Office of the Gene Technology Regulator (OGTR), Australia

**Dr. Ho-Min Jang**
Korea's National BCH, Korea Research Institute of Bioscience & Biotechnology

**PRESENTERS**

**Dr. Donald J. MacKenzie**
Executive Director, Institute for International Crop Improvement, Donald Danforth Plant Science Center USA

**Dr. Peter Thygesen**
Principal Regulatory Scientist, Office of the Gene Technology Regulator, Australia

**Dr. Florida Carino**
Retired Professor of Chemistry, University of the Philippines Diliman and Member, Biosafety Committee, Department of Science & Technology, Philippines

**PANELLISTS**

**Dr. Abraham J. Manalo**
Professorial Lecturer, National College of Public Administration and Governance (NCPAG), University of the Philippines

**Dr. Kodi Isparan Kandasamy**
Group Science Advisor, (Asia Plantation Capital Berhad)

**Dr. Vibha Ahuja**
Chief General Manager, Biotech Consortium India Limited, India

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## WEBINAR SERIES ON

## Applications of Gene Editing in Sustainable Agriculture and Food Security in Asia-Pacific Region

### WEBINAR 3

### Enabling Policies for Genome Editing in Agriculture

Date:
August 18, 2021, 10.30 AM - 12.30 PM
ICT (Bangkok time)

Registration
https://zoom.us/meeting/register/tJAqdumsqDooGNApndwbg1Zl6ldtYcsrLM5y

**CHAIRPERSON**

**Dr. William D. Dar**
Secretary,
Department of Agriculture,
Philippines

**PRESENTERS**

**Dr. Kanokwan (May) Chodchoey**
Executive Director,
Asia and Pacific Seed Association
(APSA), Thailand

**Mr. Fabrice Mattei**
Patent Attorney and
Co-head, Rouse's Patent Group

**PANELLISTS**

**Dr. Roland Schafleitner**
Flagship Program Leader - Vegetable Diversity and Improvement, World Vegetable Centre, Taiwan

**Dr. Okjae Koo**
Director, Business Development, Plant and Animal Genome Editing, ToolGen Inc. Co-founder, PLANTEDIT

**Prof. Masashi Tachikawa**
Nagoya University, Japan

**Dr. Ravi Khetarpal**
Executive Secretary, Asia Pacific Association of Agricultural Research Institutions

# Notes

For further information, please contact

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