UNIVERSITY OF LATVIA
FACULTY OF MEDICINE AND LIFE SCIENCES

New Genomic Techniques: a way forward for the sustainable future of the EU agriculture

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30.01.2025.

Outline of the talk

- What are New Genomic Techniques?
- What is the current status of NGTs?
- Why is change needed in regulating NGTs?
- What's in the EC proposal?
- What are the options for regulating NGTs?

SUSTAINABLE DEVELOPMENT GOALS

Sustainable development goals and biotechnologies

BIOTECHNOLOGY DRIVES SOLUTIONS FOR SUSTAINABLE DEVELOPMENT

Breakthroughs in biotechnology can:

- Cure once incurable diseases;
- Enable rapid response to health crises;
- Improve plant health to withstand environmental stress to enhance food security;
- Promote animal health;
- Address antimicrobial resistance;
- Reduce greenhouse gases; and
- Develop food ingredients that provide micronutrients and fortified food solutions to help end hunger.

The International Council of Biotechnology Associations (ICBA) partners with its national authorities and international organizations to unleash the tools of biotechnology to overcome global challenges.

https://www.bio.org/sites/default/files/2019-11/ICBA%202019_SDG%20Brochure_Final.pdf

GMO definition

Directive 2001/18/EC on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, Article 2:

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

Within the terms of this definition:

(a) **genetic modification occurs at least through the use of the techniques** listed in Annex I A, part 1;

(b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification

Methods of genetic modification

Directive 2001/18/EC Annex IA

Techniques of genetic modification referred to in Article 2(2)(a) are inter alia:

(1) **recombinant nucleic acid techniques** involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;

(2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;

(3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally

Exemptions

Directive 2001/18/EC Annex IA

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

  (1) **mutagenesis**,

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

Press and Information

Court of Justice of the European Union
PRESS RELEASE No 111/18
Luxembourg, 25 July 2018

Judgment in Case C-528/16
Confédération paysanne and Others v Premier ministre and Ministre de l'Agriculture, de l'Agroalimentaire et de la Forêt

Organisms obtained by mutagenesis are GMOs and are, in principle, subject to the obligations laid down by the GMO Directive

However, organisms obtained by mutagenesis techniques which have conventionally been used in a number of applications and have a long safety record are exempt from those obligations, on the understanding that the Member States are free to subject them, in compliance with EU law, to the obligations laid down by the directive or to other obligations

Genome edited (targeted mutagenesis) organisms are GMO

30.01.2025.

New Genomic Techniques

- Genetically modified organisms are defined in the Directive 2001/18/EC and the appropriate national regulations of the EU member states
- 2001 is the baseline – methods of genetic modification developed after 2001 are considered to be New Genomic Techniques (NGT)
- Methods of traditional random mutagenesis are covered by the exemption in GMO Directive, while the new techniques for targeted genome editing including CRISPR-Cas9 are regulated as GMOs

- https://www.efsa.europa.eu/en/topics/new-genomic-techniques

Criteria of equivalence of NGT1 plants to conventional plants (Annex I)

A NGT plant is considered equivalent to conventional plants when it differs from the recipient/parental plant by no more than 20 genetic modifications of the types referred to in points 1 to 5, in any DNA sequence sharing sequence similarity with the targeted site that can be predicted by bioinformatic tools.

(1) substitution or insertion of no more than 20 nucleotides;

(2) deletion of any number of nucleotides;

(3) on the condition that the genetic modification does not interrupt an endogenous gene:

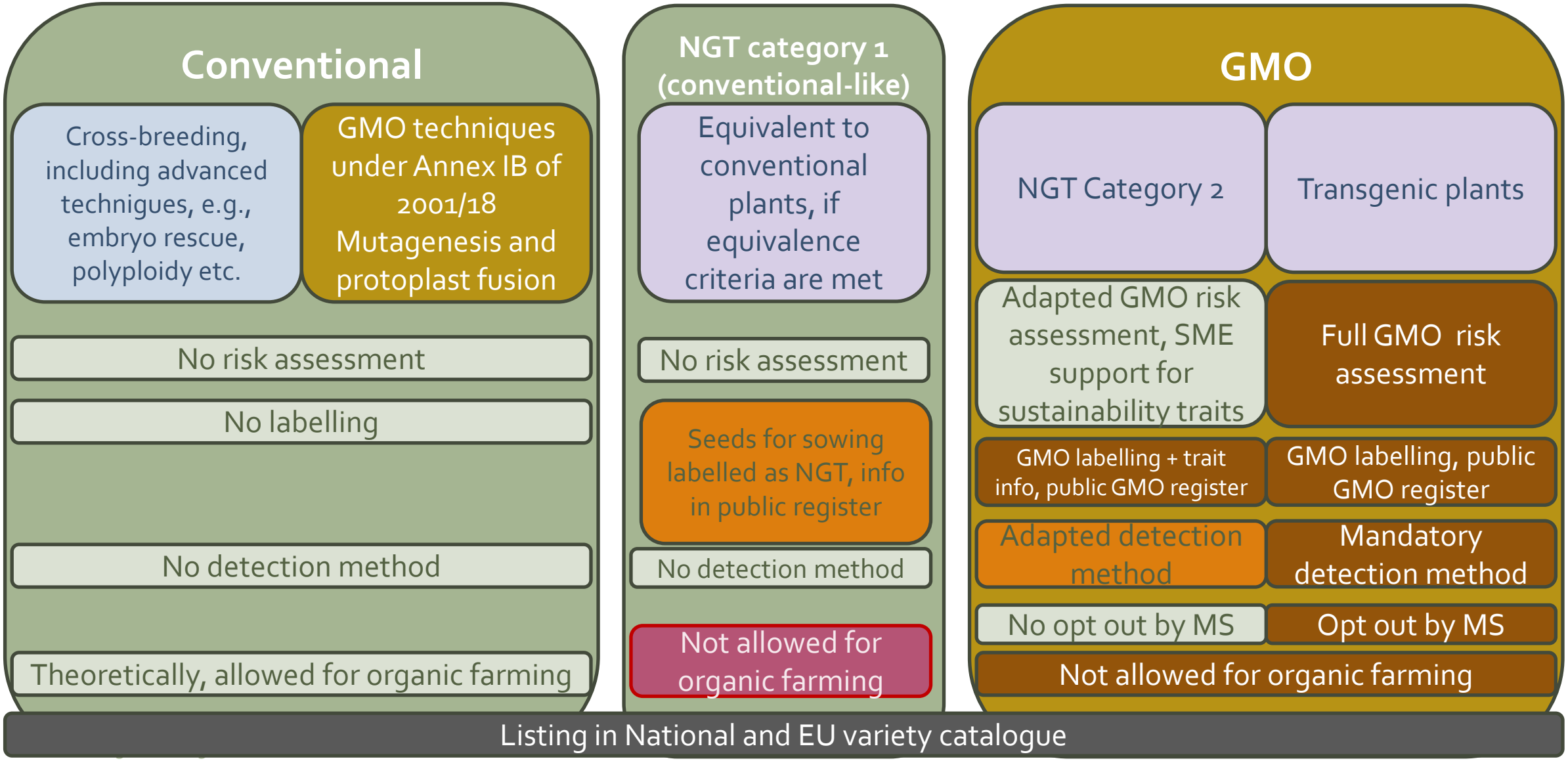
(a) targeted insertion of a contiguous DNA sequence existing in the breeder's gene pool;

(b) targeted substitution of an endogenous DNA sequence with a contiguous DNA sequence existing in the breeder's gene pool;

(4) targeted inversion of a sequence of any number of nucleotides;

(5) any other targeted modification of any size, on the condition that the resulting DNA sequences already occur (possibly with modifications as accepted under points (1) and/or (2)) in a species from the breeders' gene pool.

Plant product classification



Timeline of the new legislative proposal for NGTs

SDN discovery

Nobel prize in chemistry for CRISPR-Cas9 (2020)

ECJ ruling 2018

EC publishes a study on new genomic techniques (2021)

Preparatory work by the EC and the EFSA on SDNs, gene drives (2020), synthetic biology, in vitro mutagenesis (2021) , cis- and intragenesis (2022), criteria for RA of targeted mutagenesis (2022)

EFSA opinion on NGT equivalence criteria (ANSES, 2024)

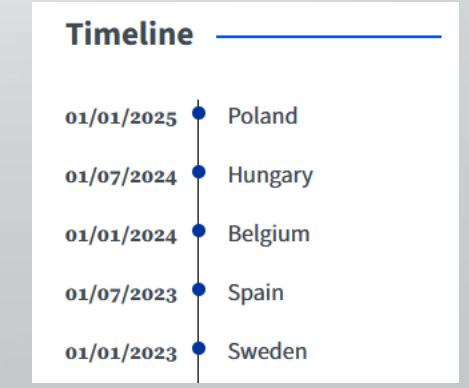
EC revises the proposal in response to MSs (2023)

EC new legislative proposal on NGTs creating NGT1 and NGT2 categories (2023)

Trilogue among the EC, the European Parliament and the Council of the EU begins

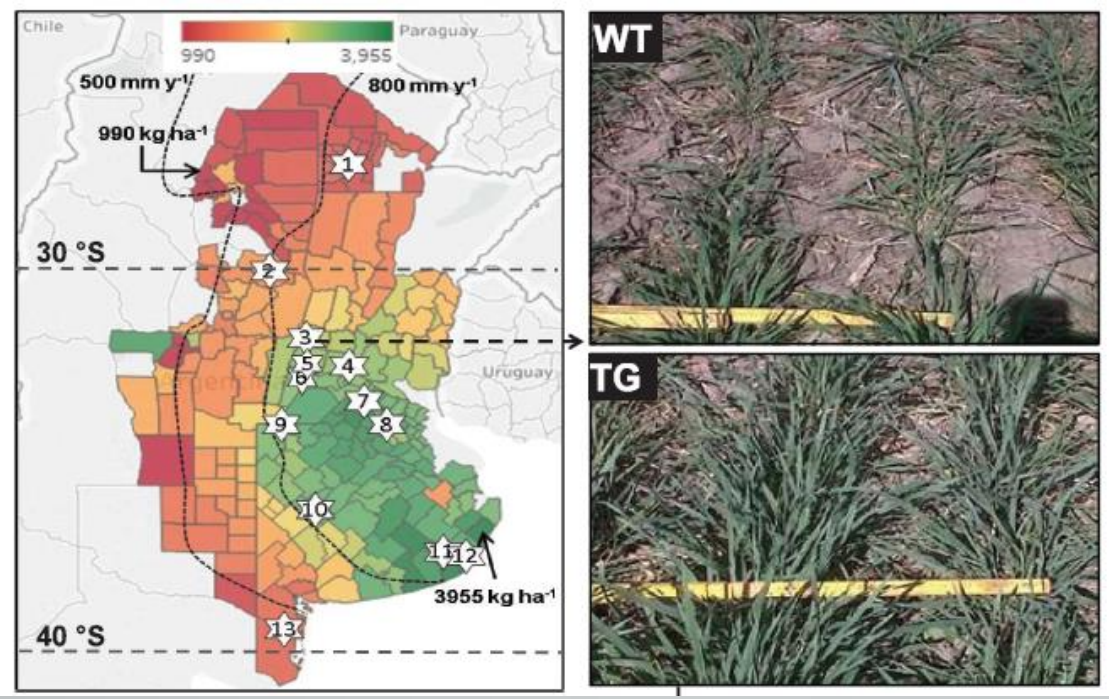
The Council maintains discussions, but does not reach consensus (2025)

EP adopts the report on NGT proposal (as prepared by ENVI) (2024)



The presidency of the Council of the EU

Exmaples of genetic engineering for abiotic stress tolerance



Journal of Experimental Botany, Vol. 70, No. 5 pp. 1669–1681, 2019
doi:10.1093/jxb/erz037 Advance Access Publication 6 February 2019
This paper is available online free of all access charges (see https://academic.oup.com/jxb/pages/openaccess for further details)

RESEARCH PAPER

Field-grown transgenic wheat expressing the sunflower gene *HaHB4* significantly outyields the wild type

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Received 14 September 2018; Editorial decision 18 January 2019; Accepted 18 January 2019

Editor: Greg Rebetzke, CSIRO Agriculture and Food, Australia

Abstract

HaHB4 is a sunflower transcription factor belonging to the homeodomain-leucine zipper I family whose ectopic expression in Arabidopsis triggers drought tolerance. The use of PCR to clone the *HaHB4* coding sequence for wheat transformation caused unprogrammed mutations producing subtle differences in its activation ability in yeast. Transgenic wheat plants carrying a mutated version of *HaHB4* were tested in 37 field experiments. A selected transgenic line yielded 6% more ($P<0.001$) and had 9.4% larger water use efficiency ($P<0.02$) than its control across the evaluated environments. Differences in grain yield between cultivars were explained by the 8% improvement in grain number per square meter ($P<0.0001$), and were more pronounced in stress (16% benefit) than in non-stress conditions (3% benefit), reaching a maximum of 97% in one of the driest environments. Increased grain number per square meter of transgenic plants was accompanied by positive trends in spikelet numbers per spike, tillers per plant, and fertile florets per plant. The gene transcripts associated with abiotic stress showed that HaHB4's action was not dependent on the response triggered either by RD19 or by DREB1a, traditional candidates related to water deficit responses. HaHB4 enabled wheat to show some of the benefits of a species highly adapted to water scarcity, especially in marginal regions characterized by frequent droughts.

Keywords: Drought tolerance, grain yield determination, HaHB4, sunflower transcription factor, transgenic wheat, water use efficiency, wheat field trials.

Introduction

Plants have evolved molecular mechanisms to deal with stress conditions, enabling their survival and reproduction. Among abiotic stress factors, drought is the major limiting constraint on agricultural productivity (Wang *et al.*, 2003). Drought tolerance has been used as a key parameter to select transgenic stress-tolerant model plants and crops (Araus and Cairns,

Plant Biotechnology Journal

Plant Biotechnology Journal (2017) **15**, pp. 207–216 doi: 10.1111/pbi.12603

ARGOS8 variants generated by CRISPR-Cas9 improve maize grain yield under field drought stress conditions

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Received 20 May 2016;
revised 6 July 2106;
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Summary

Maize *ARGOS8* is a negative regulator of ethylene responses. A previous study has shown that transgenic plants constitutively overexpressing *ARGOS8* have reduced ethylene sensitivity and improved grain yield under drought stress conditions. To explore the targeted use of *ARGOS8* native expression variation in drought-tolerant breeding, a diverse set of over 400 maize inbreds was examined for *ARGOS8* mRNA expression, but the expression levels in all lines were less than that created in the original *ARGOS8* transgenic events. We then employed a CRISPR-Cas-enabled advanced breeding technology to generate novel variants of *ARGOS8*. The native maize GOS2 promoter, which confers a moderate level of constitutive expression, was inserted into the 5′-untranslated region of the native *ARGOS8* gene or was used to replace the native promoter of *ARGOS8*. Precise genomic DNA modification at the *ARGOS8* locus was verified by PCR and sequencing. The *ARGOS8* variants had elevated levels of *ARGOS8* transcripts relative to the native allele and these transcripts were detectable in all the tissues tested, which was the expected results using the GOS2 promoter. A field study showed that compared to the WT, the *ARGOS8* variants increased grain yield by five bushels per acre under flowering stress conditions and had no yield loss under well-watered conditions. These results demonstrate the utility of the CRISPR-Cas9 system in generating novel allelic variation for breeding drought-tolerant crops.

Keywords: maize, ARGOS, CRISPR-Cas9, genome editing, drought tolerance, grain yield.

Introduction

Developing more drought-tolerant crops in a sustainable manner is one means to meet the demand of an increasing human population that will require more food, feed and fuel. Improvement in drought tolerance of crops is ultimately measured by an increase in grain yield under water-limiting conditions. The physiological processes and metabolic networks underlying drought tolerance are complicated and often difficult to delineate. Nevertheless, the phytohormone ethylene is known to play an important role in regulating plant response to abiotic stress, including water deficits and high temperature (Hays *et al.*, 2007; Kawakami *et al.*, 2010, 2013). Field studies have shown that reducing ethylene biosynthesis by silencing *1-aminocyclopropane-1-carboxylic acid synthase6* in transgenic maize plants improves grain yield under drought stress conditions (Habben *et al.*, 2014). A higher yield also can be achieved by decreasing the sensitivity of maize to ethylene (Shi *et al.*, 2015). *ARGOS* genes are negative regulators of the ethylene response and modulate ethylene signal transduction, enhancing drought tolerance when overexpressed in transgenic maize plants (Guo *et al.*, 2014; Shi *et al.*, 2015).

In addition to a transgenic approach, natural genetic variation for traits that impact drought tolerance has also been used in maize breeding programmes to improve grain yield. By applying precision phenotyping and molecular markers as well as understanding the genetic architecture of quantitative traits, maize breeders developed hybrids (AQUAmax®) with increased grain yield under drought stress conditions (Cooper *et al.*, 2014; Gaffney *et al.*, 2015). The drought tolerance in these hybrids is governed by multiple genes which individually have small effects. Potentially, some of these key genes could be identified and altered to generate new alleles to produce a larger effect, thus enhancing the breeding process. However, until recently, generating such allelic variation with physically or chemically induced mutagenesis was a random process, which made it difficult to produce intended DNA sequence changes at a target locus. In the past few years, efficient genome editing technologies have emerged, enabling rapid and precise manipulation of DNA sequences, and setting the stage for developing drought-tolerant germplasm by editing major genes in their natural chromosomal context.

Four genome editing tools, meganucleases, zinc-finger nucleases (ZFN), transcription activator-like effector nucleases (TALEN) and the clustered regularly interspaced short palindromic repeat (CRISPR)/CRISPR-associated nuclease protein (Cas) system, have provided targeted gene modification in plants (Čermák *et al.*, 2015; Gao *et al.*, 2010; Li *et al.*, 2012, 2013; Shukla *et al.*, 2009). Among these, the CRISPR-Cas9 system is easiest to implement and is highly efficient. The system consists of a Cas9 endonuclease derived from *Streptococcus pyogenes* and a chimeric single guide RNA that directs Cas9 to a target DNA sequence in the genome. CRISPR-Cas9 genome editing is accomplished by introducing a DNA double-strand break in the target locus via Cas9, followed by DNA repair through either the endogenous imprecise nonhomologous end-joining (NHEJ) or the high-fidelity homology-directed repair (HDR) pathways. NHEJ can induce small insertions or deletions at the repair junction while HDR stimulates precise sequence alterations, including programmed sequence correction as well as DNA fragment insertion and swap, when a DNA repair template is exogenously supplied. The system has been successfully tested in staple crops, such as maize, wheat, rice and soybean (Cai *et al.*, 2015; Du *et al.*, 2016; Jacobs *et al.*, 2015; Jiang *et al.*, 2013; Li *et al.*,

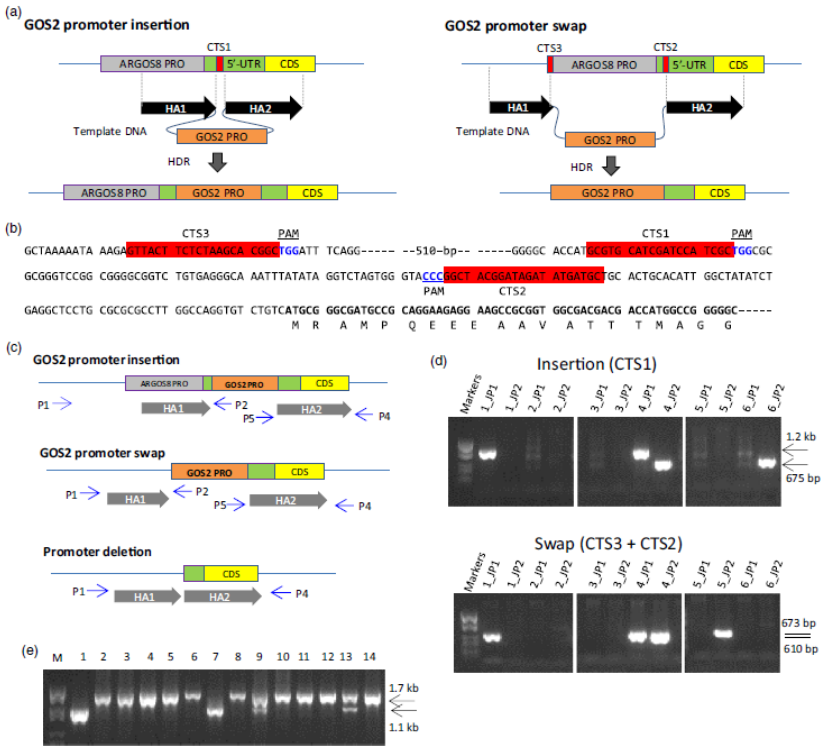


Figure 2 Editing the *ARGOS8* genomic sequence using the CRISPR/Cas9 system to generate variants with constitutive expression. (a) Schematic drawing illustrating the insertion of GOS2 PRO into the 5′-UTR of *ARGOS8* and the promoter swap. CTS, CRISPR-RNA target site; HA, homology arm; HDR, homology-directed repair; GOS2 PRO, maize GOS2 promoter and the 5′-UTR with an intron. (b) Genomic sequence of the *ARGOS8* 5′-UTR and the upstream region. The CRISPR-RNA target sites (CTS) are highlighted in red, and the protospacer adjacent motifs (PAM) are shown in blue font. The *ARGOS8* coding region is shown in bold font. (c) Diagram showing primers used in junction PCR for genotyping regenerated shoots and long PCR for amplifying and sequencing the entire modification region in homozygous plants. The relative position and direction of PCR primers (P) are indicated by arrows. P1 and P2 for the HR1 junction; P5 and P4 for the HR2 junction; P1 and P4 for the long PCR. (d) Junction PCR analysis of regenerated shoots. Agarose gel images are shown for representative regenerated shoots positive for one junction or two junctions and shoots negative in the junction PCR assay. JP1, HR1 junction PCR with the primer P1 and P2; JP2, HR2 junction PCR with P5 and P4. (e) PCR screening regenerated shoots for deletion in the *ARGOS8* locus. An agarose gel image is shown for PCR products amplified with the primer P1 and P4 in representative shoots (Lanes 1-14) generated from the *CRISPR RNA-3* and *RNA-1* transformation. M, DNA molecular weight markers.

30.01.2025.

BIOTECH UPDATES
A weekly summary of world developments in biotechnology, produced by the ISAAA Global Knowledge Center on Biotechnology direct to your inbox.
ISAAA Inc.

Japan Launches World's First Genome-Edited Tomato

March 24, 2021

Photo Source: Sanatech Seed Co.

The first direct consumption genome-edited tomato was launched in Japan by Sanatech Seed. The Japanese ministries in-charge have announced their determination that the genome-edited tomato will not be regulated as a genetically modified product.

Sanatech Seed's Sicilian Rouge High GABA tomato was developed using CRISPR-Cas9 gene editing

Gene-edited GABA-enhanced tomatoes begin shipping in Japan

Juichiro Ito | Japan Forward | November 7, 2022

Credit: Japan Forward

This month marks the start of shipments of tomatoes that control high blood pressure, the first gene-edited food to be approved by the Japanese government for distribution and sale.

...

Japan's first gene-edited food is a tomato that contains four to five times more GABA, a substance reported to be effective in controlling high blood pressure and alleviating stress, than a conventional tomato.

TABLE 2 Target genes for improvement of abiotic stress tolerance.

Abiotic stress	Target gene	Species	Stress Role	Proposed Strategy	Publication
Heat	*OspsbA*	*Oryza sativa*	Response	Upregulate	(Chen et al., 2020)
	LaHsfA2c	*Lolium arundinaceum**	Response		(Wang et al., 2017)
	OsCNGC14 OsCNGC16	*Oryza sativa*	Sensing		(Cui et al., 2020)
	SlMAPK3	*Solanum lycopersicum*	Response	Downregulate	(Yu et al., 2019)
	OsPYL1/4/6	*Oryza sativa*	Response		(Miao et al., 2018)
	SlPHYA SlPHYB1B2	*Solanum lycopersicum*	Response		(Abdellatif et al., 2022)
Cold	*EnCOR410*	*Elymus nutans*	Response	Upregulate	(Fu et al., 2016)
	AcSnRK2.11	*Agropyron cristatum*	Response		(Xiang et al., 2020)
	OsCOLD1	*Oryza sativa*	Sensing		(Ma et al., 2015)
	OsMYB30	*Oryza sativa*	Response	Downregulate	(Zeng et al., 2020)
	AtEGR2	*Arabidopsis thaliana*	Response		(Ding et al., 2019a)
	AtCRPK1	*Arabidopsis thaliana*	Response		(Liu et al., 2017c)
Drought	*CdDHN4*	*Cynodon dactylon*	Response	Upregulate	(Lv et al., 2017)
	OsSYT-5	*Oryza sativa*	Sensing		(Shanmugam et al., 2021)
	AcSnRK2.11	*Agropyron cristatum*	Response		(Xiang et al., 2020)
	OsDST	*Oryza sativa*	Response	Downregulate	(Santosh Kumar et al., 2020)
	TaSal1	*Triticum aestivum*	Response		(Abdallah et al., 2022)
	HvCBP20	*Hordeum vulgare*	Response		(Daszkowska-Golec et al., 2020)
Salinity	*ZmDHN11*	*Zea mays*	Response	Upregulate	(Ju et al., 2021)
	AcSnRK2.11	*Agropyron cristatum*	Response		(Xiang et al., 2020)
	OsOSCA1.4	*Oryza sativa*	Sensing		(Zhai et al., 2020)
	OsbHLH024	*Oryza sativa*	Response	Downregulate	(Alam et al., 2022)
	HvITPK1	*Hordeum vulgare*	Response		(Vlčko and Ohnoutková, 2020)
	OsRR22	*Oryza sativa*	Response		(Zhang et al., 2019)

*Festuca arundinacea.

Gene knock-outs for abiotic stress tolerance

Sustek-Sánchez F, Rognli OA, **Rostoks N**, Sõmera M, Jaškūnė K, Kovi MR, Statkevičiūtė G, Sarmiento C (2023) Improving abiotic stress tolerance of forage grasses – prospects of using genome editing. Frontiers in Plant Science 14

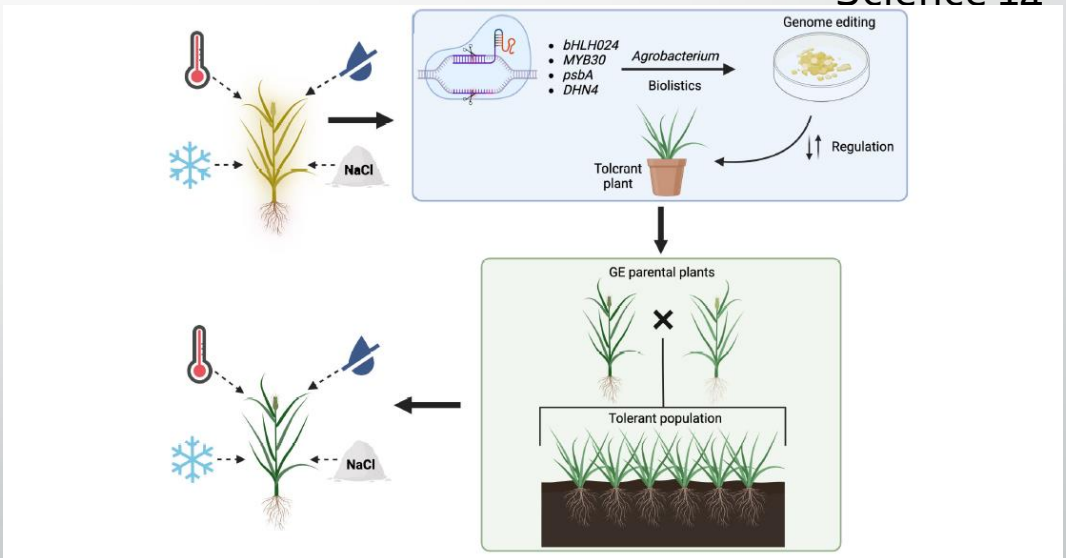


FIGURE 1
Proposed strategy for the improvement of abiotic stress tolerance in forage grasses using genome editing. Four abiotic stresses (heat, low temperature, drought, salinity) hinder the overall wellbeing of a non-tolerant grass (plant shown in yellow). Using the CRISPR-Cas system, different genes can be targeted. Agrobacterium-mediated transformation or biolistics are suitable delivery methods of the CRISPR-Cas+gRNAs complex for in-vitro culture modifications that lead towards the generation of abiotic stress tolerant plant (blue rectangle). Once tolerant parental plants are obtained (GE, gene editing), these can be crossed to produce a population able to overcome the effects of abiotic stress (green rectangle). The green plant on the bottom left represents a tolerant grass.

GeneBEcon – 6 regulatory options at a glance

1. Status Quo

- GMO-legislation stays intact
- No changes by future ECJ judgments

- Trans-, cisgenic and genome edited organisms = GMO
- Authorisation via comitology procedure

2. Use existing possibilities

- Use of leeways in current GMO legislation to facilitate the use of NGT
- Reduction of ERA-requirements
- Amendment of Reg. (EU) 503/2013

- Trans-, cisgenic and genome edited organisms = GMO

3. Regulatory differentiation of NGT plants according to their risk profiles

- GMO-legislation stays intact for transgenic organisms
- Regulatory relaxation for cisgenic & genome edited plants

- Simplified authorization for cis and GE plants
- Authorisation via comitology procedure

4. Product based approach

- Authorisation of organisms according to their traits and properties
- Risk assessment of all organisms

- Authorisation by EU authority
- Organisms are regulated by properties – no matter how they were produced

5. Foreign DNA approach

- Specific regulation only for organisms with foreign DNA*
- No risk assessment for other organisms

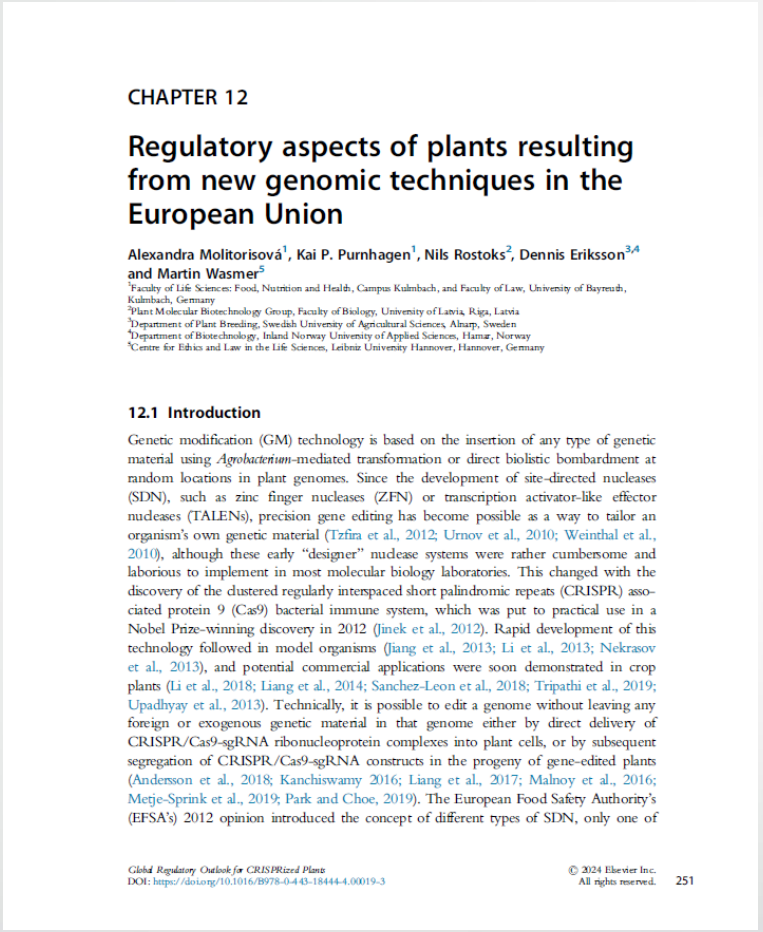
- Cisgenic and genome edited organisms:
- Official determination of lack of foreign DNA if necessary

6. REACH based approach

- Private sector responsibility
- Registration of GMOs

- Registered according to their classification: Cisgenic, transgenic, SDN-1, -2, -3, ..

Additional information



CHAPTER 12

Regulatory aspects of plants resulting from new genomic techniques in the European Union

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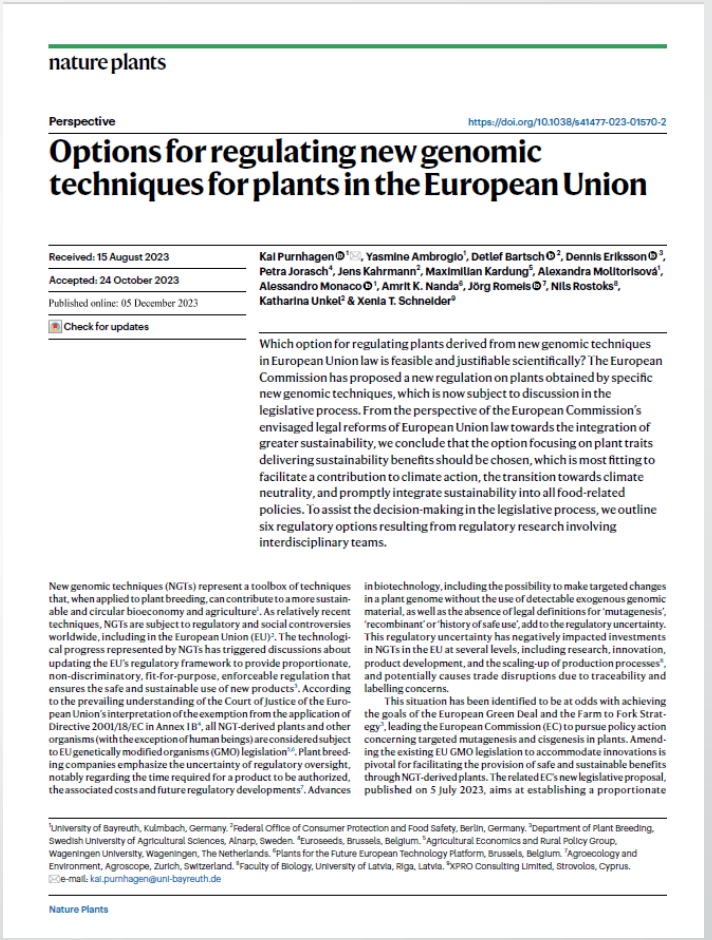
12.1 Introduction

Genetic modification (GM) technology is based on the insertion of any type of genetic material using *Agrobacterium*-mediated transformation or direct biolistic bombardment at random locations in plant genomes. Since the development of site-directed nucleases (SDN), such as zinc finger nucleases (ZFN) or transcription activator-like effector nucleases (TALENs), precision gene editing has become possible as a way to tailor an organism's own genetic material (Tzfira et al., 2012; Urnov et al., 2010; Weinthal et al., 2010), although these early "designer" nuclease systems were rather cumbersome and laborious to implement in most molecular biology laboratories. This changed with the discovery of the clustered regularly interspaced short palindromic repeats (CRISPR) associated protein 9 (Cas9) bacterial immune system, which was put to practical use in a Nobel Prize-winning discovery in 2012 (Jinek et al., 2012). Rapid development of this technology followed in model organisms (Jiang et al., 2013; Li et al., 2013; Nekrasov et al., 2013), and potential commercial applications were soon demonstrated in crop plants (Li et al., 2018; Liang et al., 2014; Sanchez-Leon et al., 2018; Tripathi et al., 2019; Upadhyay et al., 2013). Technically, it is possible to edit a genome without leaving any foreign or exogenous genetic material in that genome either by direct delivery of CRISPR/Cas9-sgRNA ribonucleoprotein complexes into plant cells, or by subsequent segregation of CRISPR/Cas9-sgRNA constructs in the progeny of gene-edited plants (Andersson et al., 2018; Kanchiswamy 2016; Liang et al., 2017; Malnoy et al., 2016; Metje-Sprink et al., 2019; Park and Choe, 2019). The European Food Safety Authority's (EFSA's) 2012 opinion introduced the concept of different types of SDN, only one of

Global Regulatory Outlook for CRISPRized Plants
DOI: https://doi.org/10.1016/B978-0-443-18444-4.00019-3

Molitorisová et al. Regulatory Aspects of CRISPR Edited Plants in EU, Elsevier book chapter



nature plants

Perspective

https://doi.org/10.1038/s41477-023-01570-2

Options for regulating new genomic techniques for plants in the European Union

Received: 15 August 2023

Accepted: 24 October 2023

Published online: 05 December 2023

Check for updates

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Which option for regulating plants derived from new genomic techniques in European Union law is feasible and justifiable scientifically? The European Commission has proposed a new regulation on plants obtained by specific new genomic techniques, which is now subject to discussion in the legislative process. From the perspective of the European Commission's envisaged legal reforms of European Union law towards the integration of greater sustainability, we conclude that the option focusing on plant traits delivering sustainability benefits should be chosen, which is most fitting to facilitate a contribution to climate action, the transition towards climate neutrality, and promptly integrate sustainability into all food-related policies. To assist the decision-making in the legislative process, we outline six regulatory options resulting from regulatory research involving interdisciplinary teams.

New genomic techniques (NGTs) represent a toolbox of techniques that, when applied to plant breeding, can contribute to a more sustainable and circular bioeconomy and agriculture[1]. As relatively recent techniques, NGTs are subject to regulatory and social controversies worldwide, including in the European Union (EU)[2]. The technological progress represented by NGTs has triggered discussions about updating the EU's regulatory framework to provide proportionate, non-discriminatory, fit-for-purpose, enforceable regulation that ensures the safe and sustainable use of new products[3]. According to the prevailing understanding of the Court of Justice of the European Union's interpretation of the exemption from the application of Directive 2001/18/EC in Annex IB[4], all NGT-derived plants and other organisms (with the exception of human beings) are considered subject to EU genetically modified organisms (GMO) legislation[5,6]. Plant breeding companies emphasize the uncertainty of regulatory oversight, notably regarding the time required for a product to be authorized, the associated costs and future regulatory developments[7]. Advances in biotechnology, including the possibility to make targeted changes in a plant genome without the use of detectable exogenous genomic material, as well as the absence of legal definitions for 'mutagenesis', 'recombinant' or 'history of safe use', add to the regulatory uncertainty. This regulatory uncertainty has negatively impacted investments in NGTs in the EU at several levels, including research, innovation, product development, and the scaling-up of production processes[8], and potentially causes trade disruptions due to traceability and labelling concerns.

This situation has been identified to be at odds with achieving the goals of the European Green Deal and the Farm to Fork Strategy[9], leading the European Commission (EC) to pursue policy action concerning targeted mutagenesis and cisgenesis in plants. Amending the existing EU GMO legislation to accommodate innovations is pivotal for facilitating the provision of safe and sustainable benefits through NGT-derived plants. The related EC's new legislative proposal, published on 5 July 2023, aims at establishing a proportionate

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Purnhagen et al. Options for Regulating New Genomic Techniques for Plants in the European Union. Nature Plants

Acknowledgments

30.01.2025.