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Swiss Expert Committee for Biosafety SECB

SECB opinion

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TEgenesis

Relevance and biological risks in consideration of Swiss and European legislation on gene technology

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1 Background and conclusion

The SECB has examined the new TEgenesis plant breeding technique and assessed it with regard to possible risks. The focus was on answering the following question:

Do plants obtained using TEgenesis differ from plants derived from classical and targeted mutagenesis, and should they be classified as genetically modified organisms (GMOs) within the meaning of Swiss gene technology legislation?

Of particular relevance here is the definition of mutagenesis and its classification for the production of genetically modified organisms.

In its considerations, the SECB also took Swiss and European legislation into account and sought to apply this to TEgenesis. The Federal Council's current views were also included in this assessment.

The SECB has thus come to the following conclusion:

In the SECB's opinion, TEgenesis should be regarded as a method of activating and accelerating a naturally occurring process rather than as classical mutagenesis technique. Therefore, plants derived through TEgenesis cannot be considered as genetically modified organisms within the meaning of the gene technology legislation. The risks associated with such plants are no greater than those of plants produced using classical plant breeding methods, including classical mutagenesis. As with all agricultural products, it is important to conduct accurate variety testing.

2 TEgenesis – a new plant breeding technique

2.1 Mutagenesis in plant breeding

Mutagenesis is the generation of changes in the genome of organisms, called mutations. This technique is used in biological and medical research as well as in plant breeding to achieve desired favourable characteristics. It alters the gene sequence being responsible for the positive or negative changes in the phenotype.

Mutation breeding programmes were first used in plant breeding as early as the 1930s. More than 3,200 plant mutant varieties from over 210 species have now been released in over 70 countries.[1] The mutagens used were in the form of radiation or chemical compounds. These techniques are now considered 'classical mutagenesis'.

However, in the early days of such breeding methods, it was not known how they would affect the organism's DNA. With random mutagenesis, as this happens with chemicals and radiation, there are multiple unpredictable changes at the level of the DNA. Therefore, apart from the desired characteristics, other undetected changes may also occur in the organism.

In 90 years of experience with random classical mutagenesis, no negative impacts have been demonstrated in humans, animals or for the environment. The procedure is therefore considered to have a 'history of safe use'. This is quite surprising, since a somewhat greater risk would have been expected here.

[1] FAO/IAEA Mutant Varieties Database

2.2 Transposable elements

Transposable elements (TEs) are naturally occurring DNA sequences that can jump from one location in the genome to another or duplicate themselves within the genome.

For Class 1 TEs, the intermediate is formed by RNA. These are therefore called retro-TEs. They replicate themselves within the genome by way of a 'copy and paste' mechanism. Class 2 TEs use a DNA intermediate, and so these are called DNA TEs. They change their position within the genome but do not replicate themselves ('cut and paste').

Although transpositions are rather seldom occurring in plants, they are sometimes triggered by naturally occurring environmental conditions. In some cases, the trigger seems to cause the plant to adapt to the changed environmental conditions.

At the genetic level such naturally occurring processes result in a change in the DNA sequence, especially insertions and deletions. In higher plants, such DNA changes have also been detected in seeds and can therefore be inherited. This need to be considered a natural evolutionary process of the plant.

The transposition of genetic elements in eukaryotic cells was first discovered in 1940–55 by Barbara McClintock[2] while studying the genetics of maize. One of her starting points was a rare mosaic colouring of the grains observed in certain maize mutants.

However, transpositions also play a role in the development of different varieties of a species. For example, S. Vezzuli[3] demonstrated in 2012 that wine varieties Pinot gris and Pinot blanc evolved from Pinot noir as a result of transpositions. In its report 'Considerations on green gene technology',[4] the SECB addresses such changes in the genetic material of conventionally bred plants.

Transpositions are therefore natural developmental steps for higher plants, and their economic value has long been recognised. They also contribute to a better understanding of the mechanisms of evolution at the DNA level.

[2] B. McClintock (1950): The Origin and Behavior of Mutable Loci in Maize: Proc. Natl. Aced. Sci, BD 36, pp. 344–355

[3] S. Vezzulli et al. (2012): Pinot blanc and Pinot gris arose as independent somatic mutations of Pinot noir: Journal of Experimental Botany, Vol. 63, No 18, pp. 6359–6369

[4] Considerations on green gene technology (in German), SECB 2012: https://www.efbs.admin.ch/inhalte/dokumentation/medienmitteilungen/Hintergrundpapier_D_121112_Internet.pdf

2.3 TEgenesis

2.3.1 Is TEgenesis a type of mutagenesis?

With TEgenesis, transpositions - meaning naturally occurring DNA changes - are induced in plants through the application of two substances. In contrast to classical chemical or physical mutagenesis, the nucleotide sequence is not changed by the action of chemicals or radiation, but by the transposable element, which is moved around the genome and integrated at another, random location in the genome. Similar changes in DNA could also be caused in plants by naturally occurring abiotic stress factors such as cold, heat or drought. Transpositions are thus part of the natural evolution process of living organisms.

In the SECB's view, TEgenesis can therefore not be considered as mutagenesis in the classical sense. Instead, it must be viewed as a process of chemical stimulation of naturally occurring biochemical processes modifying the DNA sequence within plants.

It thus differs fundamentally from targeted and classical mutagenesis, as the changes to the DNA sequence are based on a natural process.

2.3.2 Is it possible for the organisms produced in this way to also occur spontaneously in nature?

Based on the current state of knowledge, it is not possible to say conclusively whether the exact same transpositions that are triggered by chemical activation may also be triggered naturally (e.g. by environmental effects). It cannot be ruled out, however.

If these transpositions can indeed be induced naturally, the SECB is of the opinion that these plants shall not be classified as genetically modified.

On the other hand, if these changes only occur as a result of chemical stimulation, it would be difficult to classify them within the current legal framework. At best, a classification as a novel type of chemical mutagenesis process might be conceivable.

However, the organisms produced in this way should then still not be regulated as GMOs since chemical compounds were used to mobilise these transpositions, as it is the case with classical mutagenesis.

3 Mutagenesis and its legal definition as a method of gene technology – Unresolved questions and contradictions

3.1 The current situation in Europe

In its judgment of 25 July 2018,[5] the European Court of Justice states that organisms obtained by mutagenesis constitute genetically modified organisms within the meaning of the EU GMO Directive as the processes and methods of mutagenesis alter the genetic material of an organism in a way that does not occur naturally.

Furthermore, the European Court of Justice states that the GMO Directive does not apply to certain techniques of mutagenesis, specifically those which have been traditionally used in a range of applications and have long been considered safe ('history of safe use').

This judgment raises fundamental questions:

[5] Judgment of 25 July 2018 of the Court of Justice of the European Union: https://eur-lex.europa.eu/legal-content/EN/ALL/?uri=CELEX%3A62016CJ0528

1. Certain mutagenesis techniques can generate organisms that can also be grown naturally, e.g. through cross-breeding and selection. This means that organisms which can also be bred naturally are classified as GMOs only through the application of new technical mutagenesis processes. This contradicts the definition of a GMO and si adding to a situation where genetically identical organisms may or may not be classified as a GMO, depending on the method of production.
2. Additionally it is not possible to predict in advance which genetic modifications are occurring naturally and which are not. For example, pesticide resistances, which are arising due to DNA changes, are repeatedly occurring within pathogens in a natural way. They are continuously monitored in resistance monitoring.[6] Another example is the increasing number of glyphosate-resistant weeds and companion plants that are emerging under the selection pressure of constant glyphosate applications in agriculture.[7]
3. The use of radiation and mutagenic chemicals is considered safe. However, the judgment of the European Court of Justice does not explain how the safety of these processes is proven. It is also unclear whether all mutagenic chemicals are considered safe or only those which have previously been used and from which new commercial plant varieties have been created.

3.2 The current situation in Switzerland

The definition of genetically modified organisms is different in Swiss legislation:

1. The Gene Technology Act[8] (GTA) defines genetically modified organisms as follows:

   GTA Art. 5 para. 2

   "Genetically modified organism means organisms in which the genetic material has been altered in a way that does not occur under natural conditions by crossing or natural recombination."

2. However, the Release Ordinance[9] (RO) defines genetically modified organisms slightly different by excluding certain methods:

   RO Art. 3 let. d

   "Genetically modified organisms means organisms in which the genetic material has been altered by methods of gene technology in accordance with Annex 1 in a way that does not occur under natural conditions by crossing or natural recombination, as well as pathogenic or alien organisms that have also been genetically modified."

   RO Annex 1 Definition of Gene Technology Methods, Art. 3

   "Self-cloning of non-pathogenic organisms and the following methods shall not be regarded as methods of gene technology, as long as they are not used in association with recombinant nucleic acid molecules or genetically modified organisms:

   a. mutagenesis"

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6 European and Mediterranean Plant Protection Organization (EPPO): Activities on resistance to PPPs (eppo.int)

7 C. Boerboom & M. Owen, Facts About Glyphosate-Resistant Weeds: https://www.extension.purdue.edu/extmedia/gwc/gwc-1.pdf

8 Gene Technology Act, SR 814.91 https://www.fedlex.admin.ch/eli/cc/2003/705/en

9 Release Ordinance, SR 814.911 https://www.fedlex.admin.ch/eli/cc/2008/614/en

In its press release of 30 November 2018,[10] the Swiss Federal Council notes that the extent to which plants produced by the new gene technology processes should or should not be considered genetically modified organisms is currently unclear. At the same time, it states that the existing legislation is to be adapted on a risk basis.

The draft version (20 April 2020) of the Federal Council's 'Message on the extension of the moratorium on marketing genetically modified organisms; opening of the consultation procedure' says on page 2: "On 18 November 2018 the Federal Council stated that the new gene technology methods fall under the existing gene technology legislation. It thus shares the opinion of the European Court of Justice."

In contrast, the explanatory report on the amendment to the Gene Technology Act (Extension of the moratorium on marketing genetically modified organisms) states in section 1.3: "The Federal Council has taken note of the discussion paper, which already states that the new gene technology methods fall under the existing gene technology legislation. At this stage, it rejects the call to create the legal basis to exempt certain genome-edited plants from the application of the GTA."[11]

3.3 Considerations of the SECB

In a strict interpretation of the GTA only, without taking into account the definition of the Release Ordinance (RO), organisms produced by classical mutagenesis methods developed in the 1930s must be classified as genetically modified organisms. These methods produce organisms that do not occur under natural conditions through cross-breeding or natural recombination.

However, such an interpretation is not really useful, since many plant varieties currently being cultivated and available on the market would then have to be reclassified as genetically modified varieties.

On the other hand, according to the definition in the Release Ordinance, and in line with current practice, plants obtained by classical mutagenesis without the use of recombinant genetic material are not subject to gene technology legislation. It follows that this rule must also apply to recent mutagenesis procedures, as long as neither recombinant nucleic acids nor GMOs are used in these procedures.

It should be noted that the term 'history of safe use' is not explicitly used in Swiss law. This contrasts with the judgment of the European Court of Justice, where the classical mutagenesis methods covered by this term are completely excluded from the provisions governing gene technology.

The SECB is of the opinion that any mutagenesis procedure should be assessed in accordance with the prevailing Swiss laws and ordinances. It regrets that the Federal Council, in its dispatch on the extension of the moratorium, was guided only by the judgment of the European Court of Justice.

From the SECB's point of view, the current legislation appears confusing and does not provide the necessary legal certainty. The legislation must therefore be adapted without delay, in line with the current state of the art and taking account of the latest scientific risk-based findings.

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[10] Press release of 30 November 2018 on new gene technology methods (available in German, French and Italian): https://www.admin.ch/gov/de/start/dokumentation/medienmitteilungen.msg-id-73173.html

[11] Explanatory report on the amendment to the Gene Technology Act (Extension of the moratorium on marketing genetically modified organisms); available in German, French and Italian: https://fedlex.data.admin.ch/eli/dl/proj/6020/69/cons_1, Bericht

4 Risk assessment

Unlike conventional classical mutagenesis, the newer mutagenesis methods are much more targeted and have little or no scattering. Moreover, the type of mutation can be more precisely defined. Therefore, from a risk assessment point of view, it can be assumed that the organisms produced by these newer procedures present a lower risk potential for humans, animals and the environment than if they were obtained by classical mutagenesis.

Strictly speaking, however, TEgenesis is not a form of mutagenesis: it is based on the enhanced activation of already existing natural processes of epigenesis in the plant. It seems reasonable to assume that plant varieties produced in this way could also arise spontaneously in nature or could be obtained using classical breeding and mutagenesis methods. The only difference is that it would take considerably longer to achieve the desired results using conventional breeding methods. From a scientific point of view, there is no discernible increase in the risk potential when using TEgenesis compared to classical breeding and mutagenesis.

As the SECB has already pointed out in its report on new plant breeding methods,[12] it is important to assess whether plant varieties obtained through new technologies such as TEgenesis raise new safety issues compared to the outcome of conventional breeding methods. This is not the case here. As with classical breeding methods, those plants with the desired characteristics are then further bred in the subsequent selection process. Product control and plant variety testing are still necessary in any case.

Finally, the plants obtained through TEgenesis should not be classified as GMOs within the meaning of the Gene Technology Act since neither recombinant nucleic acids nor genetically modified organisms are used or produced with this novel method of mutagenesis.

[12] SECB report on new plant breeding techniques, May 2015 (in German): https://www.efbs.admin.ch/inhalte/dokumentation/Ansichten/D_Bericht_EFBS_Neue_Pflanzenzuchtverfahren.pdf

5 Conclusions and recommendations

1. TEgenesis shall not be classified as a method of genetic modification within the meaning of the legislation on gene technology. Thus, plants produced by means of TEgenesis are not genetically modified organisms either. In the SECB's view, they may therefore be used for experimental releases without requiring a licence under the RO.
2. The European Court of Justice is of the opinion that classical mutagenesis does not pose a risk to humans, animals or the environment on the basis that it has been used for a long time ('history of safe use'). In the case of newer methods which are more targeted than classical mutagenesis, it can be assumed that these too do not pose any great risk to humans, animals or the environment.
3. From a scientific point of view, there is no reason why a targeted modification of the genome should entail a higher biological risk than a method that displays scattering and where it is not possible to predict which changes will occur in the genome. The SECB is firmly in favour of assessing the safety of the product – in this case the plant variety – and not just the method by which it was produced.
4. In the SECB's view, the current legislation is contradictory with regard to the definition of genetically modified organisms and gene technology methods. It thus fails in its purpose of ensuring the legal certainty required for new gene technology processes. This applies in particular to the evaluation of targeted mutagenesis methods. There is an urgent need for legal clarification in this regard.
5. Innovations in the field of plant breeding, as exemplified by TEgenesis, are to be strongly encouraged. The SECB recognises the need to shorten breeding times for new varieties, in view of climate change and related crises posing a threat to global food security, and cautions against excessive regulation of innovative breeding methods, including gene technology.
6. The SECB expressly recalls the conclusions of the national scientific research programme NRP59 to the effect that, from a risk-based perspective and even after many years of cultivation of genetically modified plants worldwide, no unacceptable risks to humans, animals or the environment have been identified to date. In our own study 'Biological Risks in Switzerland'[13] we show that plants developed through breeding methods using gene technology pose a negligible risk.

[13] Biological Risks in Switzerland, SECB 2019: https://www.efbs.admin.ch/inhalte/dokumentation/Ansichten/Biologische_Risiken_Schweiz/EFBS_Biologische-Risiken_Schlussbericht_E.pdf