



On the ECJ Ruling regarding mutagenesis and the Genetically Modified Organisms Directive

Brussels, 19.2.2019

The European Plant Science Organisation (EPSO) considers that the ruling of the European Court of Justice (ECJ) on organisms obtained by mutagenesis (case C-528/16) disregards scientific evidence. The ruling subjects plants obtained by recent mutagenesis techniques such as CRISPR/Cas9-mediated genome editing to extensive pre-market risk assessment whereas plants produced by older, less precise mutagenesis techniques are exempted. In sharp contrast, there is broad scientific consensus that unintended DNA alterations produced by genome editing are of the same type but orders of magnitude less frequent than those produced by older methods such as EMS or radiation mutagenesis.

Genome editing is not the only answer to current challenges of agriculture and society, but it represents an important tool for harnessing plant science knowledge toward a future-ready agriculture, for allowing Europe and the EU to play a leading role in innovative plant science, and to contribute to the bioeconomy by boosting the performance of underutilised plant species and biological resources. In the drive to achieve sustainable development goals, no useful tool should be neglected. Consequently, EPSO supports a science-based change to the present European legislation and proposes to establish a legislation adapted to future technological developments by increasing emphasis on product-based risk assessment. Meanwhile, further tangible commitment is needed to support, inform and communicate about innovative plant science and its societal role.

What is the context of the ruling? As expressed in its first reaction¹, the European Plant Science Organisation (EPSO) considers that the ruling of the European Court of Justice (ECJ) in case C-528/16, which classifies plants obtained by recent techniques such as CRISPR/Cas9-mediated genome editing as genetically modified organisms (GMO), which are not exempt from the provisions of the EU GMO Directive, disregards scientific evidence. As laid down in the report of the Scientific Advice Mechanism², genetically and phenotypically similar plants obtained by more recent techniques are "not expected to present significantly different risks" than those produced by older techniques which have "a history of safe use" according to the ruling. Therefore, EPSO proposes to revise Directive 2001/18/EC, to establish a regulation adapted to future technological developments and to shift towards a more-product-based risk assessment.

What is the scope of the ruling? In its ruling on case C-528/16, the ECJ gave a legal answer to a legal question. It clarified that modern mutagenesis techniques, including genome editing, are in the scope of Directive 2001/18/EC, and how it needs to be

applied. It did not answer the question whether it is appropriate to apply the provisions of Directive 2001/18/EC – the legal design of which is based on knowledge from the last century – to more recently developed techniques without taking into account present knowledge on genome evolution, structure and plasticity. The ruling generated the paradoxical legal situation that two plants, which are identical are not regulated in the same way. The plant obtained by targeted genome editing is subject to extensive pre-market risk evaluations but not the plant produced by chemical mutagenesis or irradiation followed by breeding to eliminate off-target effects. EPSO calls for a fact-based legislation taking into account all available scientific knowledge, which avoids unequal treatment.

What is the scientific context of genome editing? Mutation and selection are not only the driving forces of evolution, but also of 10 000 years of agriculture. Adaptation of plants to changing climates and domestication of wild species for human needs have been based on genetic variation due to mutations. Different ways to provoke and exploit mutations have been employed throughout human agricultural history, and genome editing mediated by CRISPR/Cas9 or other techniques is yet another tool to serve a need as ancient as humankind. A dispassionate scientific comparison of genome editing with conventional breeding and established mutagenesis breeding has been published by scientific experts appointed by the European Commission to its High Level Scientific Advice Mechanism. In their Explanatory Note on New Techniques in Agricultural Biotechnology, these experts demonstrate, on the basis of peer-reviewed publications that genome editing is more precise, since the site and/or nature of the mutation is pre-determined without causing more unintended mutations in the genome than conventional breeding. In comparison to older, untargeted mutation breeding techniques the number of unintended mutations is strongly reduced. In line with this analysis, in a recent statement³ the same experts underline the scientific shortcomings of the ruling and recommend revising the existing GMO Directive "to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification". EPSO fully supports this statement. This critical analysis of the ruling is also supported by hundreds of European plant scientists who signed a position paper entitled "Regulating genome-edited organisms as GMOs has negative consequences for agriculture, society and economy" and which calls upon all European authorities "to quickly respond to this ruling and alter the legislation"⁴.

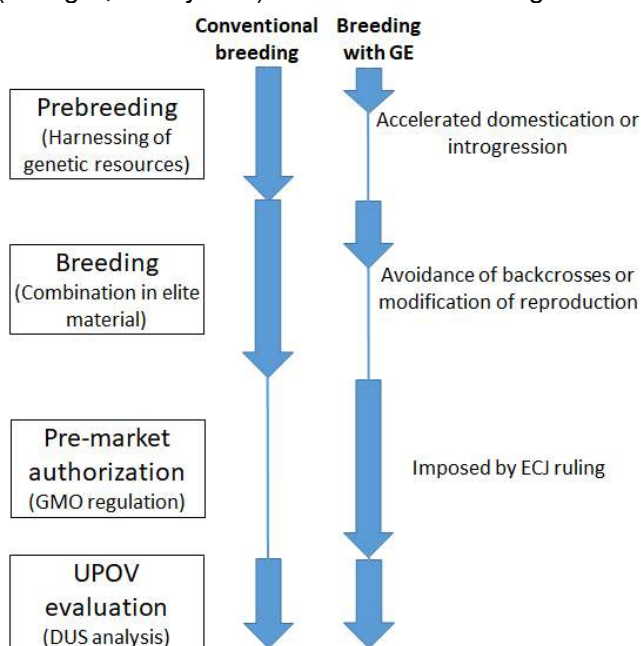
What are the potential benefits of modern mutagenesis techniques? Genome editing permits the efficient translation of biological knowledge of genes into traits useful for a sustainable agriculture. It is not the only answer to current challenges of agriculture, such as the overuse of pesticides and inputs, climate change, crop monocultures or the desire for improved human food. However, together with other levers such as the reduction of waste, innovative culture systems or precision agriculture, genome editing can contribute to meeting and managing these challenges by enhancing genetic progress towards more diverse, better adapted and yet high yielding plant varieties. Proof of concept has been provided for disease resistance (fungi, bacteria, viruses), abiotic stress tolerance (drought, salt), herbicide tolerance, yield parameters, biofortification and low-allergen food^{5,6}.

In addition, genome editing has high potential to streamline different steps in plant breeding (Fig. 1). During early steps of the process (pre-breeding), desirable traits of wild relatives of crop species can be harnessed either by accelerated domestication^{7,8,9}, or by genome editing of pertinent genes for conferring, for example, disease resistance in the crop species¹⁰. In both cases, potentially deleterious effects of neighbouring genes (genetic drag) as well as lengthy and costly introgression steps are avoided. Similarly, the actual breeding can be sped up by avoidance of backcrosses or the modification of reproductive processes¹¹. Shorter breeding times enhance reactivity to emerging threats

to agriculture such as the arrival of new diseases, the reappearance of ancient diseases or more severe weather conditions (drought, heavy rain) due to climate change.

Fig. 1:

Comparison of conventional and genome editing (GE) breeding in Europe. The timelines of key steps in plant breeding are indicated by arrows. UPOV, International Union for the Protection of New Varieties of Plants; DUS, Distinct, uniform and stable.



Finally, genome editing is likely to boost the economic performance of underutilised plants, contributing to increased diversity in agriculture and nutritional security. EPSO is in favour of activating all available tools in an integrated fashion to face the worldwide challenges of agriculture.

How do non-European countries regulate genome editing? Several South American countries (Argentina, Brazil, Chile and Colombia), as well as Israel, base their regulation on the definition of living modified organisms (LMO) in the Cartagena Protocol on Biosafety, signed by 103 countries including the European Union¹². Contrary to the insertion of transgenes, the small insertions, deletions or modifications of nucleotides in genome edited plants are not considered as a "novel combination of genetic material" and are consequently regulated just like conventional varieties. Japan also adheres to the Cartagena Protocol and might follow this path. Other countries such as Australia and India are considering changes to their legislation regarding genome-edited plants, since such plants in principle would have to be treated as GMOs due to their existing national definitions. A very clear stand for the deregulation of genome-edited plants comes from the USA in the USDA Statement on Plant Breeding Innovation issued by Secretary Sonny Perdue in March 2018, who wants to "avoid additional regulation of plants indistinguishable to those developed by traditional techniques". Consequently, genome-edited plants with deletions or single base-pair substitutions (including complete null segregants), and even with insertions from compatible relatives, are not regulated as GMOs.

Without any judgement as to the scientific soundness of the different national regulations, EPSO regrets this disharmony of positions around the world, which raises complex questions concerning the declaration, detection and traceability of genome-edited plants and products, not only for world trade, but also for exchange and usage of genetic resources from outside the EU for cross breeding. As stated in the recent Explanatory Note of the JRC¹³, mutations induced by genome editing technologies cannot be unequivocally distinguished from natural mutations, nor can they be differentiated from those induced by conventional mutagenesis techniques. While recognizing that harmonization of legislation, let alone regulation, is extremely difficult, EPSO

nonetheless would urge legislators to harmonize regulations as much as possible using science-based approaches.

How to implement a science-based legislation? To take into account present scientific knowledge, legislators may either update existing regulatory texts, or create a novel framework. A key point is to clarify and harmonize the scope of the EU GMO legislation with the international legal situation. Currently the EU definition of "GMO" differs between different pieces of EU legislation as well, which is confusing.

Legal experts are developing different lines of thought on how to obtain such a clarification and harmonization within Directive 2001/18/EC. Some alternatives are:

(i) explicitly adding modern mutagenesis methods such as CRISPR/Cas9-mediated genome editing to the exemptions in Annex I B, as proposed by the Dutch competent authorities;

(ii) further defining "mutagenesis" in a way that includes modern mutagenesis methods such as CRISPR/Cas9;

(iii) clarifying the precise meaning of "altered in a way that does not occur naturally" in the definition of "genetically modified organism (GMO)".

Other experts propose that Europe could follow countries adhering to the definition of living modified organisms (LMOs) of the Cartagena Protocol on Biosafety, which has been implemented in Europe by EU Regulation (EC) 1946/2003 without harmonizing the EU GMO definition with the Cartagena LMO definition. Finally, Europe could switch to a problem oriented and more proportionate legislation. For example, the Canadian system defines "plants with novel traits", where only the novelty of the trait and its potential to affect the specific use and safety of the plant with respect to the environment and human health is evaluated, no matter whether it is introduced using biotechnology, mutagenesis, or conventional breeding techniques.

In the meantime, an adapted, scientifically sound (i.e. proportionally simplified) risk assessment of gene edited plants should be considered when applications are submitted for approval to the European Commission¹⁴.

What are our concerns as plant scientists? The ruling of the ECJ presents a considerable drawback for the future of innovative plant science and its societal benefits in Europe. Genome editing has rapidly become an indispensable tool in publicly funded academic research, and translation of the gained biological knowledge into applications enhancing the durability and flexibility of agriculture will likely be impeded by the ruling¹⁵. Public scientists will tend to either neglect more applied research or avoid genome editing techniques for applied projects. Others will be tempted to seek international collaborations for field trials in countries with less burdensome legislations. Private companies are likely to delocalize their research and development in genome editing to countries where the technology is deregulated. Moreover, the ruling writes a question mark into future policies for research funding in plant science. All of this will lead to a strongly reduced expertise in genome editing in Europe, while the technology will be widely applied in the rest of the world.

EPSO support for creating a future-ready regulation: Notwithstanding the technical option retained, EPSO supports a science-based revision of the present European legislation establishing a more proportionate product-based risk assessment¹⁶.

EPSO offers to collaborate with policy makers to develop an appropriate regulation to enable the European public sector, small- and medium-sized companies and farmers to contribute more comprehensively to food and nutritional security and to use all available tools to reduce the environmental impact of agriculture. EPSO is also willing to contribute to the societal debate on genome editing and to communicate in a fact-based and yet accessible manner about innovative plant science and its societal role.

This statement was developed by the EPSO Agricultural Technology Working Group led by Peter Rogowsky, Frank Hartung and Ralf Wilhelm with input from the EPSO Representatives and Board, based on the discussions and upon request of the EPSO General Meeting 2018.

References

¹ On the ECJ ruling regarding mutagenesis and the Genetically Modified Organisms Directive – First reaction.

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² New techniques in agricultural biotechnology.

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³ A scientific perspective on the regulatory status of products derived from gene editing and the implications for the GMO directive.

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Useful links

Court of Justice of the EU: Judgment in Case C-528/16, 25.7.2018. [English Press Release](#); [Ruling in English](#);

Court of Justice of the EU: Advocate General's Opinion in Case C-528/16, 18.1.2018. [English Press Release](#); [Opinion in English](#)

Court of Justice of the EU: [Case C-528/16](#)

EC: [Explanatory Note on New Techniques in Agricultural Biotechnology](#) from EC's High Level Scientific Advice Mechanism, 28.4.2017

EC [news alert](#) Commission's top scientific advisers publish explanatory note on new techniques in agricultural biotechnology, 28.4.2017

<https://epsoweb.org>

EPSO [Working Group on Agricultural Technologies](#):

Statements drafted by this group and approved by the EPSO representatives are for instance:

- EPSO updated statement on [Crop Genetic Improvement Technologies](#), 12.01.2017
- EPSO: [First reaction on the Advocate General's Opinion regarding mutagenesis and the Genetically Modified Organisms Directive](#), 18.1.2018
- EPSO: [Opinion on the SAM Explanatory Note on New Techniques in Agricultural Biotechnology](#), 15.9.2017
- EPSO: [Synthetic Biology should not be confused with the application of new breeding techniques](#), updated statement, 30.8.2017
- EPSO: [Comment on the report of the Ad Hoc Technical Expert Group on Synthetic Biology](#), 8.3.2018, [original report of the AHTEG and all submitted comments](#).

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