European Commission

Statement by the Group of Chief Scientific Advisors

A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive

On 25 July 2018, the Court of Justice of the European Union ('the Court') decided that organisms obtained by the new techniques of directed mutagenesis are genetically modified organisms (GMOs), within the meaning of the Directive 2001/18/EC on the release of genetically modified organisms into the environment ('GMO Directive')[1,2], and that they are subject to the obligations laid down by the GMO Directive.

New techniques of directed mutagenesis include gene editing such as CRISPR/Cas9 methodologies. The legal status of the products of such techniques was uncertain, because it was unclear whether they fell within the scope of the GMO Directive.

These techniques enable the development of a wide range of agricultural applications and the ethical, legal, social and economic issues of their use are discussed intensively. The European Commission's Group of Chief Scientific Advisors (the 'Chief Scientific Advisors')[3] recognises the complex nature of these debates, which touch upon people's beliefs, values, and concerns, as well as the underpinning science.

The mandate of the Chief Scientific Advisors is to provide scientific advice to the European Commission. Therefore, following our explanatory note on 'New Techniques in Agricultural Biotechnology' (SAM, 2017a), we have examined the GMO Directive taking into account current knowledge and scientific evidence.

1. The Ruling of the Court of Justice

On request by the French *Conseil d'État*, the Court was asked to determine whether organisms obtained by mutagenesis[4] should be considered GMOs and which of those organisms are exempt according to the provisions of the GMO Directive. In particular, the Court was asked to determine whether organisms obtained by new directed mutagenesis techniques are exempt from the obligations imposed by the GMO Directive, as are those obtained by conventional, random mutagenesis techniques that existed before the adoption of the Directive, or are regulated like those obtained by established techniques of genetic modification (ETGM).

The Court declared that organisms produced by directed mutagenesis techniques/methods should be considered GMOs within the meaning of the GMO Directive and subject to the relevant requirements. In this regard, the Court concluded that only organisms obtained by means of techniques/methods of mutagenesis, which have conventionally been used in a number of

[1] https://eur-lex.europa.eu/legal-content/en/TXT/?uri=CELEX%3A32001L0018
[2] https://curia.europa.eu/jcms/upload/docs/application/pdf/2018-07/cp180111en.pdf
[3] https://ec.europa.eu/research/sam/index.cfm?pg=hlg

[4] Mutagenesis encompasses both random mutagenesis and directed mutagenesis. Random mutagenesis is also often referred to as 'conventional mutagenesis' or 'traditional mutagenesis', whereas 'directed mutagenesis', 'site-directed mutagenesis' or 'precision mutagenesis' are often used as synonyms for 'targeted mutagenesis'. The Court used the term 'directed mutagenesis'.

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applications and have a long safety record, are exempt. The Court also considered that 'risks linked to the use of those new techniques/methods of mutagenesis might prove to be similar to those which result from the production and release of a GMO through transgenesis'[5]. The Court further reasoned that these new techniques 'make it possible to produce genetically modified varieties at a rate and in quantities quite unlike those resulting from the application of conventional methods of random mutagenesis'.

New techniques resulting in directed mutagenesis can alter a DNA sequence precisely at one or more targeted positions in the genome. For an overview of different types of gene editing see our explanatory note on 'New Techniques in Agricultural Biotechnology' (SAM, 2017a) including a description of the CRISPR/Cas9 system (Jinek et al., 2012). Random mutagenesis, which has been used extensively in plant breeding since the 1960s (SAM, 2017a), alters an organism's genome at multiple positions in a non-targeted way by treatment with a chemical mutagen or irradiation. ETGM, which have been used in agriculture since the 1980s, can be used to introduce DNA sequences from other organisms.

The background for the Court ruling was an action brought before the French *Conseil d'État* by the French agricultural union *Confédération Paysanne* together with eight other associations. This action contested the French legislation according to which organisms obtained by mutagenesis are not, in principle, considered as being the result of genetic modification, and asked for a ban on the cultivation and marketing of herbicide-tolerant oilseed rape varieties obtained by mutagenesis. The claimants argued that such herbicide-resistant seed varieties pose a risk to the environment and health.

2. Issues and questions arising from the ruling and the application of the GMO Directive

The GMO Directive states that 'the regulatory framework for biotechnology should be reviewed so as to identify the feasibility of improving the consistency and efficiency of that framework' (Recital 63). As detailed below, in view of the Court's ruling, it becomes evident that new scientific knowledge and recent technical developments have made the GMO Directive no longer fit for purpose. Moreover, the GMO Directive gives rise to more general problems, in particular with regard to the definition of GMOs in the context of naturally occurring mutations, safety considerations, as well as detection and identification.

2.1. Definition of GMOs in the context of naturally occurring mutations

The definition of GMOs contained in the GMO Directive dates back to 1990. According to this definition, a GMO is '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'.[6] In the light of current scientific knowledge, it is worth reflecting whether the concept of 'naturalness' is useful when deciding on regulatory requirements for organisms with an altered genome.

Mutations occur naturally without human intervention (SAM 2017a). They arise spontaneously

[5] The term 'transgenesis' is often used to refer to the introduction of a gene or genes from a distinct species into a cell or an organism, but can also be interpreted in a broader sense to refer to the introduction of an exogenous gene or genes into cells or organisms leading to the transmission of the input gene (transgene) to successive generations. This can include the introduction of (a) gene(s) from the same or a sexually compatible species. The present statement collectively refers to these techniques as established techniques of genetic modification (ETGM).

[6] https://eur-lex.europa.eu/resource.html?uri=cellar:303dd4fa-07a8-4d20-86a8-0baaf0518d22.0004.02/DOC_1&format=PDF

during cell division or are triggered by environmental factors such as ultraviolet light or viral infections, and can be either neutral, harmful or confer a competitive advantage to the organism. This is the underlying mechanism of natural evolution. From the time of the adoption of the GMO Directive until now, owing to progress in analytical methods, extensive scientific evidence has been accumulated on spontaneously occurring genetic alterations. These include point mutations (changes within a single letter in the genomic DNA), insertions, deletions and rearrangements of the genome, as well as the acquisition of exogenous genetic material across species or even kingdoms (e.g. (Kyndt et al., 2015)). Therefore, if referred to in the legislation, the concept of 'naturalness' should be based on current scientific evidence of what indeed occurs naturally, without any human intervention, in organisms and in their DNA.

2.2 Safety considerations

Changes introduced by random mutagenesis are usually more drastic than those resulting from gene editing techniques, and include not only numerous point mutations, but also deletions and major rearrangements of genome fragments. The resulting mutant organisms (in this case plants) require lengthy screening of the organisms' characteristics to identify the few mutants that carry a novel desirable feature and do not present any unwanted features. Despite this lengthy screening process, the ultimately selected end products are likely to carry additional mutations beyond the ones resulting in the desired trait, each of which can be considered to be an 'unintended effect'[7]. Such unintended effects can be harmful, neutral or beneficial with respect to the final product.

In 2001, when the Directive 2001/18/EC was adopted, gene editing technologies were not yet being applied to agricultural organisms. For example, the CRISPR/Cas9 system was first described only in 2012 (Jinek et al., 2012). Gene editing techniques can produce specific alterations at precise locations in the genome ranging from point mutations through to the targeted deletion or insertion of a gene, of parts of a gene or of other functional DNA sequences. Because of their precision, these gene editing techniques produce fewer unintended effects (Khandagale & Nadaf, 2016; SAM, 2017a) than random mutagenesis techniques. In addition, the end product is better characterised with respect to specific mutation(s) in the targeted position(s).

Because unintended effects will occur less frequently in gene edited products, these products are potentially safer than the products of random mutagenesis[8]. Recently more progress has been made to further increase the efficiency and precision, and thus the safety of the gene-editing techniques (Yin, Gao, & Qiu, 2017).

The Court has argued that new varieties can be produced at a much higher rate and in larger quantities by the directed mutagenesis techniques than by conventional methods of random mutagenesis. Targeted mutagenesis is more efficient than random mutagenesis or other conventional breeding techniques, and can speed up the process of generating desired varieties. However, the greater precision of the directed mutagenesis techniques,

[7] As explained on page 32 of the Explanatory Note on 'New Techniques in Agricultural Biotechnology' (SAM, 2017a) two different types of unintended effects can occur during breeding: (1) unintended changes and (2) unintended effects of the intended changes. Random mutagenesis results in numerous unintended changes. In the case of gene editing, the unintended changes are often referred to as 'off-target effects'.

[8] As emphasised in the explanatory note on 'New Techniques in Agricultural Biotechnology' (SAM, 2017a) the frequency of unintended effects does not allow direct conclusions regarding safety to be drawn as unintended effects can be neutral, harmful or beneficial. They therefore need to be assessed case by case. However, the occurrence of unintended effects is often raised in public discussions in relation to concerns about the safety of gene editing products. In general, the precision of the gene editing methods is expected to reduce some sources of unintended effects. Therefore, they have the potential to produce fewer possibly harmful unintended effects at product level.

which enable better control of the product's characteristics, is a much more important factor to consider in safety deliberations than the rate at which products are generated.

In addition, gene editing techniques result in fewer intermediate and unwanted 'varieties' compared to random mutagenesis techniques.

The GMO Directive refers to both the process used in genetic engineering and the product resulting from the use of such techniques (Abbott, 2015), but it is often interpreted as being based only on the production technique rather than the characteristics of the resulting product (Sprink, Eriksson, Schiemann, & Hartung, 2016). An example of this is the consideration of the 'long safety record' of random mutagenesis which is introduced by Recital 17 of the GMO Directive as a criterion for deciding whether products generated with different techniques of genetic modification are exempt from its obligations or not. In scientific terms what is more relevant is, whether or not the products have a long safety record, rather than the techniques used to generate them.

In that context, it is important to recognise that the concerns put forward by the *Confédération Paysanne* about the risk of herbicide resistant seed varieties to the environment and health are not addressed by subjecting organisms produced by directed mutagenesis to the obligations of the GMO Directive. This is because herbicide resistant seed varieties can in principle be produced by all mutagenic procedures including ETGM, new directed mutagenesis techniques, random mutagenesis, as well as other conventional breeding methods. It is not primarily the modified crop that constitutes the potential ecological risk, but rather the use of the herbicide and the overall production system associated with herbicide use (Bioökonomierat, 2018). To answer the question whether herbicide resistant seed varieties constitute a risk to health and environment, **the features of the final product itself must be examined regardless of the underlying technique used to generate that product.**

As described in our explanatory note (SAM, 2017a), the safety of an organism is determined by multiple factors such as the specific characteristics of the organism, the environment in which it is cultivated, the agricultural practices used, and exposure to human beings and animals rather than by the technique used for its production. Hence, the risks of a product are determined by these factors and therefore logically should be assessed in the same way independently of whether they are produced by conventional breeding techniques, random or directed mutagenesis, or by ETGM. Consequently, the current approach does not properly respect the motivation behind the precautionary principle of ensuring product safety. From the above it follows that the regulatory framework for GMOs should put much more emphasis on the features of the end product, rather than on the production technique. As long as this is not the case, situations can arise where two products are identical, but because of different methods used in their production, they would have to meet completely different regulatory requirements

2.3 Detection and identification issues

The ability of gene editing techniques to precisely introduce mutations identical to those originating spontaneously or through random mutagenesis has important consequences for the detection of gene edited products, as described in our explanatory note (SAM, 2017a). Depending on the mutation type and the context in which it is used, it will be difficult and sometimes impossible for applicants to provide a detection method for gene edited products which will meet regulatory requirements (Casacuberta & Puigdomènech, 2018), for instance in the case of point mutations.

Detection becomes even more difficult when there is no prior knowledge concerning the organism under investigation, whether authorised or not, in particular regarding the introduced genetic changes and/ or a suitable detection method (SAM, 2017a). Competent authorities will be faced with such circumstances, for instance, when organisms arrive on the EU market, which have been authorised under regulatory systems outside the EU with differing regulatory requirements. There can be no analytical approach for detecting and quantifying all possible gene edited products. Therefore it cannot be excluded that products obtained by directed mutagenesis will enter the European market undetected. It will be impossible to identify whether the mutations have occurred spontaneously or were introduced by human intervention, or to attribute them to a specific technique such as random mutagenesis or directed mutagenesis, particularly given that in some cases the final product will be identical to that generated by other procedures (Sprink et al., 2016). However, as mentioned before, the safety of a product is determined by its characteristics and not by the way it was generated. **Therefore, the impossibility of distinguishing between spontaneously occurring mutations and different types of human interventions is a major issue from a regulatory point of view.**

A document, currently under preparation by the European Network of GMO Laboratories together with the European Commission's Joint Research Centre, will look in more detail at the issues related to detection, identification and quantification than we do here.

3. Possible consequences

The ruling of the Court can be expected to have important consequences for European citizens – both consumers and farmers. It may also have impacts on international trade and cooperation with developing countries, and very likely, also on the EU research and innovation landscape. The consequences need to be analysed and discussed elsewhere, as this statement focusses on scientific issues related to the application of the GMO Directive to the new directed mutagenesis techniques, but we make some comments here to inform those discussions.

In legal terms, products of gene editing can be authorised in the EU according to the GMO Directive. However, meeting the obligations of the GMO Directive implies cost- and labour-intensive pre-market evaluations and a long duration of the approval process, which are difficult and onerous to bear, particularly by small and medium enterprises[9]. This may diminish incentives for investment, negatively affect research and innovation in this field, and limit the commercialisation of gene edited products (Bioökonomierat, 2018; Georges & Ray, 2017).

In addition, the obligations, imposed by the GMO Directive, on traceability and labelling of GMOs entering the European market will be very difficult to implement and control due to issues related to the detection, identification and quantification of gene edited products described above (section 2.3). This will become more difficult when exporting countries start to market varieties that they have already decided not to regulate. An example is the case of gene edited mushrooms developed to have a reduced tendency to brown [10] (Georges & Ray, 2017; Waltz, 2016).

Environmental applications of gene editing technologies could enable novel approaches to conservation, bioremediation, the control of invasive species, and the protection of biodiversity (Shukla-Jones, Friedrichs, & Winickoff, 2018). Hindering EU

[9] For a description of the length and cost of the regulatory process, see for instance (Bioökonomierat, 2018; Callaway, 2018; Stokstad, 2018).
[10] USDA. Reply to Request for Confirmation that Transgene-Free, CRISPR-Edited Mushroom Is Not a Regulated Article 2016. https://www.aphis.usda.gov/biotechnology/downloads/reg_loi/15-321-01_air_response_signed.pdf

progress in this field may prevent the use of gene editing technologies for environmental applications as well as for sustainable food production[11], including the reduction of food scarcity in developing countries. Lost opportunities could include producing plants with resistance to pests and diseases, reducing the use of pesticides and fertilizers, generating resilience to harsh weather conditions, or enhancing nutrients in foods (Haque et al., 2018; Georges & Ray, 2017; Palmgren et al., 2015). Several gene edited crops and horticultural plants with novel features, such as healthier nutrient composition, are already in development which have the potential to provide immediate direct benefits to the consumer (for an overview of applications of gene editing in crops, vegetables and fruit see e.g. Khandagale & Nadaf, 2016; Modrzejewski, Hartung, Sprink, Krause, & Kohl, 2018; Modrzejewski, Hartung, Sprink, Krause, Kohl, et al., 2018).

It is a concern that countries in the developing world exporting feed and food to the EU might not benefit from gene edited crops if they follow the EU authorisation practices, as some of them currently do. No single breeding technique alone can provide a magic bullet for solving the problem of unsustainable food production and food scarcity in the world. However, gene- editing has the potential to contribute to food security, which is particularly relevant given the growing world population and climate change (Haque et al., 2018; Jones, 2015). In view of the above, we make some proposals regarding the way forward in the following section

4. Further reflections and proposals

There is danger that unless the EU improves the regulatory environment for products of gene-editing, it will be left behind in this field, which could also diminish EU influence on ongoing debates at the international level with respect to specific applications and regulatory processes. Further research and innovation in this area will help better understanding of possible risks and benefits for society, the environment, agriculture and the economy. There is a need to improve EU GMO legislation to be clear, evidence-based, implementable, proportionate and flexible enough to cope with future advances in science and technology in this area. To achieve this, **we recommend revising the existing GMO Directive to reflect current knowledge and scientific evidence, in particular on gene editing and established techniques of genetic modification.** This should be done **with reference to other legislation relevant to food safety and environmental protection**.

We acknowledge that there are strongly held views in the debate regarding the regulation of GMOs, based on a range of differing underlying values, ethical, legal and social issues, and that may lead to other options being preferred. In this context, it should be noted that the European Commission has requested further guidance by the European Group on Ethics in Science and New Technologies (EGE) on ethical issues raised by such technologies.

Moreover, **it is essential to promote a broad dialogue with relevant stakeholders, and the public at large.** Indeed, we have already urged that a more general inclusive discussion should be initiated on how we want our food to be produced in Europe (SAM, 2017b, 2018). Any change to the existing GMO legislation should make use of new, participatory forms of social dialogue (Bioökonomierat, 2018). In doing so, it is important to take account of the highest possible protection of health and environment and the creation of a favourable regulatory environment for innovation, so that society can benefit from new science and technology.

In addition, we conclude that there is a need for robust and independent evidence to be provided in a systematic and transparent way to the Court when

[11] One of the Sustainable Development Goals (SDGs) to which the EU has subscribed

dealing with complex scientific issues. Factors other than scientific evidence are and should be considered in policy-making as well as in jurisdiction. However, when reasons other than scientific evidence inform decision making, such as those based on ethical, legal, social and economic considerations, these should be clearly identified and communicated as such in a transparent way. At the same time, relevant and robust scientific evidence should be provided to inform decision-making and good regulation. This is essential to generate good policy and regulation, to maintain public trust in science, and to reduce the potential reputational risk to the EU, if it appears that the EU is not employing the best scientific evidence to generate good public policy. We stand ready to provide further scientific advice to the European Commission on the subjects outlined above should the College of Commissioners wish to have such advice.

Glossary

CRISPR/Cas9 - the abbreviation for 'clustered regularly interspaced short palindromic repeats and CRISPR-associated protein 9'. It is one of the most popular gene editing techniques and is derived from bacteria.

Directed mutagenesis – also referred to as 'targeted' or 'site-directed' or 'precision mutagenesis'; introduces one or several deliberate change(s) in the genome directed at a specific site. Includes gene-editing techniques such as CRISPR/ Cas9.

DNA - Abbreviation for deoxyribonucleic acid. DNA is a biological polymer that constitutes the genetic material of all known organisms, some organelles (including mitochondria and chloroplasts) and some viruses. In cells, DNA usually occurs in the form of a double helix formed by very long complementary strands arranged in an antiparallel way.

End product – In the context of this statement: the final organism obtained by a breeding technique, such as a crop plant as opposed to intermediate products which are obtained as an intermediate step in the production of an end product.

Established Techniques of Genetic Modifications (ETGM) - Techniques for the production of transgenic organisms comprising the introduction of an exogenous gene or genes into cells, which leads to the transmission of the input gene (transgene) to successive generations.

Exogenous – Produced outside of; originating from, or due to, external causes.

Gene editing - also called genome editing, is a group of mutation technologies that allow modification of genetic information by adding, removing, or altering DNA sequences at a specific location in the genome in a targeted way.

Genotype - The genotype corresponds to the DNA sequence of a cell, and therefore of an organism or individual, which determines, together with epigenetic and environmental factors, stable and heritable characteristics (phenotype) specific for that cell/organism/individual.

GMO - is the acronym for Genetically Modified Organism. According to EU legislation, it 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.

Off-target mutation - Any change in the genome with respect to a defined wild type, made to a genetic sequence in another location than the desired target. Off target mutations can occur in sequences identical or similar to the target. These mutations can be silent (i.e. cannot be associated with any change in phenotype), either because the DNA sequence affected is in the non-coding part of the genome, or because the specific change does not alter the function of a coding sequence.

Phenotype - The visible appearance of an organism (with respect to one or more traits) which reflects the interaction of a given genotype with a given environment. See: genotype.

Point mutation - a mutation affecting only one nucleotide (building blocks of DNA) in a DNA sequence**.**

Mutagenesis - is a process by which the genetic information of an organism is changed resulting in (a) mutation(s). Random mutagenesis techniques are based on using irradiation or chemical treatment of organisms or cells to generate random mutations. Directed mutagenesis techniques, including genome editing, allow for making site-specific mutations in a targeted manner.

Random mutagenesis – also referred to as 'conventional' or 'traditional mutagenesis'; refers to the process of introducing mutations to organisms in a random fashion and thus is non-specific. Random mutagenesis involves exposing organisms to a mutagen for a period of time and selecting for the organisms with the desired features. The mutagens can be either physical mutagens like UV radiation or chemical mutagens like alkylating agents.

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