

The Status under EU Law of Organisms Developed through Novel Genomic Techniques

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In a ruling on 25 July 2018, the Court of Justice of the European Union concluded that organisms obtained by means of techniques/methods of mutagenesis constitute GMOs in the sense of Directive 2001/18, and that organisms obtained by means of techniques/methods of directed mutagenesis are not excluded from the scope of the Directive. Following the ruling, there has been much debate about the possible wider implications of the ruling. In October 2019, the Council of the European Union requested the European Commission to submit, in light

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Authors have been closely involved in the negotiations of Directive 90/220/EEC and of its successor Directive 2001/18.

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of the CJEU ruling, a study regarding the status of novel genomic techniques under Union Law. For the purpose of the study, the Commission initiated stakeholder consultations early in 2020. Those consultations focused on the technical status of novel genomic techniques.

This article aims to contribute to the discussion on the legal status of organisms developed through novel genomic techniques, by offering some historical background to the negotiations on the European Union (EU) GMO Directives as well as a technical context to some of the terms in the Directive, and by analysing the ruling. The article advances that (i) the conclusion that organisms obtained by means of techniques/methods of mutagenesis constitute GMOs under the Directive means that the resulting organisms must comply with the GMO definition, ie the genetic material of the resulting organisms has been altered in a way that does not occur naturally by mating and/or natural recombination; (ii) the conclusion that organisms obtained by means of techniques/methods of directed mutagenesis were not intended to be excluded from the scope of the Directive is not inconsistent with the negotiation history of the Directive; (iii) whether an organism falls under the description of “obtained by means of techniques/methods of directed mutagenesis” depends on whether the genetic material of the resulting organisms has been altered in a way that does not occur naturally by mating and/or natural recombination. Finally, the article offers an analysis of the EU GMO definition, concluding that for an organism to be a GMO in the sense of the Directive, the technique used, as well as the genetic alterations of the resulting organism, must be considered.

I. INTRODUCTION

The foundation for the regulatory framework for biosafety in the EU was established in 1990 with the adoption of two Directives, one pertaining to the release of genetically modified organisms (hereafter “GMOs”) and one pertaining to the contained use of genetically modified micro-organisms.¹ In 1997, these Directives were complemented by the Novel Food Regulation.² In the years that followed, this regulatory framework was adjusted and expanded upon. The current overall regulatory framework consists of several Directives and Regulations, supplemented by implementing rules as well as by recommendations and guidelines on specific aspects.³

The Regulations and Guidelines refer to the GMO definition in Directive 2001/18 (hereafter “the Directive”).⁴ This Directive requires prior authorisation for the deliberate release of GMOs for placing on the market and for other purposes, such as field trials. Article 2 of the Directive provides the definitions of key terms of the regulatory framework, such as the GMO definition. Article 3, in combination with Annex IB, of the Directive exempts certain categories of GMOs from the Directive’s provisions: ie organisms obtained through techniques/methods of mutagenesis and organisms obtained through the cell fusion of plant cells of organisms that can exchange genetic material by traditional breeding methods.

¹ Many of the concepts underlying the EU legislation can be traced back to the 1986 OECD publication “Recombinant DNA Safety Considerations”, commonly referred to as the “Blue Book”, and its associated OECD Council Recommendation <www.oecd.org/redirect/dataoecd/43/34/40986855.pdf>.

² Regulation of the European Parliament and of the Council (EC) 258/97 concerning novel foods and novel food ingredients [1997] OJ L43/1.

³ For an overview see: “GMO Legislation” (Food Safety – European Commission, 17 October 2016) <ec.europa.eu/food/plant/gmo/legislation_en>.

⁴ Directive of the European Parliament and of the Council (EC) 2001/18 on the deliberate release into the environment of genetically modified organisms [2001] OJ L106/1.

In a case referred by the French Conseil d'État,⁵ the Court of Justice of the European Union (hereafter: "the Court") in July 2018 concluded that organisms obtained by means of techniques/methods of mutagenesis constitute GMOs within the meaning of the Directive. It further clarified that only organisms obtained through conventional chemical or radiation induced random mutagenesis methods are excluded from the scope of the Directive as a result of the exemption of Article 3 *inuncto* Annex IB.

There have been many articles, papers and events discussing – often fiercely – the possible wider implications of the ruling of the Court,⁶ whereby many commentators concluded that the ruling means that *all* genome-edited organisms fall under the GMO definition. The present article argues that such a conclusion reads too much into the judgment and advances a more modest reading of the Court's ruling.⁷

That the precise implications of the Court's ruling are far from settled is highlighted by request of the Council of the European Union (hereafter: "the Council") to the Commission, in October 2019, to submit to it a study regarding the status of novel genomic techniques under Union Law. The Council further requested the Commission to submit a proposal, if appropriate in view of the outcomes of the study, or otherwise to inform the Council on other measures required as a follow-up to the study.⁸ To that effect, the Commission initiated targeted stakeholder consultations in early 2020.⁹ Those consultations focused on the technical status and impact of novel genomic techniques.

This article provides a contribution to the debate on the legal status of organisms obtained through novel genomic techniques. To this end it first provides a critical analysis of the Court's ruling (section II). Subsequently, the legal status of organisms developed through novel genomic techniques is addressed by analysing the GMO definition in the Directive (section III). Where relevant, the sections are complemented with the historical background on the negotiation of the Directive and the technical context of some of the terms used in the Directive. Finally, the article identifies a way forward by presenting recommendations and conclusions (section IV). To be clear, the article does not argue that the Court erred in *Confédération*

⁵ For the detailed wording of the French court's questions, see Case C-528/16, *Confédération paysanne and others v Premier ministre and Ministre de l'agriculture, de l'agroalimentaire et de la forêt* [2018], ECLI:EU:C:2018:583, para 25.

⁶ A snapshot of the variety of articles, papers and events can be found on: Plant Genetic Resources International Platform (PGRIP), "The EU Court Case on Mutagenesis (C-528/16)" (*PGRIP*) <www.pgrip.org/the-eu-court-case-on-mutagenesis-c-528-16/>.

⁷ In an earlier issue of the EJRR Somsen discussed this case before, but focused mainly on the question submitted to the Court, ie the scope of the exemption to the Directive. See H Somsen, "Scientists Edit Genes, Courts Edit Directives: Is the Court of Justice Fighting Uncertain Scientific Risk with Certain Constitutional Risk?" (2018) 9 *European Journal of Risk Regulation*, pp 701–718. In contrast, the present article addresses the possible wider implications of the ruling on the scope of the GMO definition itself.

⁸ Council Decision (EU) 2019/1904, requesting the Commission to submit a study in light of the Court of Justice's judgment in Case C-528/16 regarding the status of novel genomic techniques under Union law, and a proposal, if appropriate in view of the outcomes of the study [2019] OJ L293/103.

⁹ J Binns, "EC Study on New Genomic Techniques" (*Food Safety – European Commission*, 23 January 2020) <ec.europa.eu/food/plant/gmo/modern_biotech/new-genomic-techniques_en>.

paysanne, and neither does it propose to change the GMO definition in the Directive. Instead the article highlights that in *Confédération paysanne* the Court only ruled on the scope of the mutagenesis exemption. The challenge thus remains to determine the precise scope of the GMO definition itself, and on this the article argues that under the existing definition both process (genomic techniques employed) and product (genetic alteration realised) need to be cumulatively met.

II. THE COURT'S RULING ON MUTAGENESIS IN *CONFÉDÉRATION PAYSANNE*

The debate that followed the Court's ruling focused almost exclusively on the potential wider implications of the ruling for the EU's regulatory regime for GMOs. Before engaging in that debate, it is useful and necessary to go back to the ruling and identify what the Court said (and, crucially, what it did not say).

1. The Court's findings

In *Confédération paysanne* the French Conseil d'État asked the Court, among other things, the following questions:¹⁰

1. Do organisms obtained by mutagenesis constitute GMOs within the meaning of Article 2 of the Directive?
2. Does the exemption of Article 3 in combination with Annex IB point 1 of the Directive only apply to organisms obtained by conventional chemical or radiation induced random mutagenesis methods that existed before the adoption of the Directive?

In response to the first question of the French Conseil d'État, the Court confirmed in paragraph 54 of the ruling that "Article 2(2) of Directive 2001/18 must be interpreted as meaning that organisms obtained by means of techniques/methods of mutagenesis constitute GMOs within the meaning of that provision".

This conclusion of the Court is consistent with the negotiation history of the Directive (see Box 1) and follows directly from its text, ie organisms can only be exempted from the Directive if they were GMOs to begin with. As Advocate General (AG) Bobek stated in his opinion "it would be illogical to exempt certain organisms from the application of the directive if those organisms could not be characterised as GMOs in the first place".¹¹

¹⁰ Case C-528/16, *supra*, note 5, para 54.

¹¹ Opinion of Advocate General Bobek in Case C-528/16, ECLI:EU:C:2018:20, para 62.

Box 1. Historical background – mutagenesis in the Directive

The Court's conclusion that organisms obtained by mutagenesis constitute GMOs under Directive 2001/18 is consistent with the negotiation history of the Directive and of its predecessor Directive 90/220. Those negotiations started in the late 1980s with the recognition of the fact that techniques other than recombinant DNA (which had been the main focus since the early 1970s) can also result in genetic alterations that would not be likely to occur in nature, such as macro-injection and cell fusion. Once the negotiations on the GMO definition had reached an advanced stage, it was recognised that plants developed through chemical or radiation induced random mutagenesis would also fall under the description of genetic alterations that do not occur through mating and natural recombination, because the simultaneous occurrence of very large numbers of mutations goes beyond what happens naturally. Recognising that crops developed through chemical and radiation induced random mutagenesis have a long safety record, some Member States were of the view that organisms developed through chemical or radiation induced random mutagenesis should be excluded from the GMO definition, while other Member States and the Commission felt that such organisms technically fall under the definition but should be exempted from the provisions of the Directive. The latter approach was followed in Directive 90/220.^{12,13}

Note: In the Cartagena Protocol on Biosafety (CPB), which was adopted in 2000, the approach taken was to leave organisms developed through techniques used in traditional breeding outside the scope of the definition of Living Modified Organisms (LMOs). The negotiations of the CPB were conducted around the same time as the review and revision of Directive 90/220. With the LMO definition of the CPB having been agreed in 1999, it was suggested that the EU GMO definition should be aligned explicitly with the CPB LMO definition, but this suggestion was not followed.

In response to the question from the French Conseil d'État related to the scope of the exemption of Annex IB, the Court concluded that:

Article 3(1) of Directive 2001/18, read in conjunction with point 1 of Annex IB to that directive and in the light of recital 17 thereof, must be interpreted as meaning that only organisms obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of that directive.¹⁴

The consideration underlying this conclusion is that:

Article 3(1) of Directive 2001/18, read in conjunction with point 1 of Annex IB to that directive, cannot be interpreted as excluding, from the scope of the directive, organisms obtained by means of new techniques/methods of mutagenesis which have appeared or have been mostly developed since Directive 2001/18 was adopted.¹⁵

¹² It is important to recognize that Art 3 in combination with Annex IB exempts certain categories of organisms developed by certain techniques, and that it does not exempt those techniques as such. Similarly, while the Directive regulates the release of certain organisms (i.e. GMOs), it does not regulate techniques.

¹³ Despite that, the French Government followed in its national legislation the approach of excluding organisms developed through conventional mutagenesis from the definition of GMO. See Art D531-2 of the French Code de l'Environnement.

¹⁴ Case C-528/16, *supra*, note 5, para 54.

¹⁵ *ibid*, para 51.

Box 2. Historical background of the mutagenesis exemption

The Court's conclusion is not inconsistent with the discussions during the negotiations of Directive 90/220 between the Member States and the Commission, because the only types of mutagenesis that were discussed at the time were techniques/methods of chemical or radiation induced random mutagenesis.

Note: The Court's reference to Recital 17 is pertinent. Recital 17 provides: "This Directive should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record." This recital reflects the thinking behind biosafety regulation worldwide since the mid-1980s: techniques of genetic modification are not considered to carry inherent risks, but they can allow for the formation of new genetic combinations that are unlikely to occur in nature or through conventional breeding. Consequently, the existing mechanisms, such as variety registration systems, may not be sufficient to conclude that the resulting organisms containing such new genetic combinations are as safe as their conventional counterparts. Therefore, in many countries biosafety regulation has been placed "on top of" the existing systems. Risk assessment under such regulations focuses on evaluating whether the new genetic combinations pose safety concerns. Consequently, categories of GMOs in which that "newness" or "novelty" is replaced by experience of safe use would no longer need the same level of additional oversight. Although this was also the thinking at the time of the negotiations in the late 1980s for Directive 90/220, it was not explicitly reflected in that Directive. Recital 17 was added by Directive 2001/18.

NB: This same thinking is also reflected in Article 7.4 of the CPB, which states that the so-called "Advanced Informed Agreement" procedure of the CPB shall not apply to living modified organisms that have been identified as being unlikely to have adverse effects.

This part of the ruling has raised two types of questions: (i) has the Court arrived at a logically sound conclusion and (ii) what are the possible wider implications of this part of the ruling? On the first question, different views have been expressed. For instance, Somsen noted that "[f]or the Court to state that Annex IB 'cannot' be interpreted as excluding new mutagenesis techniques from the scope of the Directive is rather bold, given that this is precisely what a literal interpretation would suggest it should do".¹⁶ On the other hand, one could argue that chemical or radiation induced random mutagenesis was indeed the only form of mutagenesis that was discussed at the time of the negotiations on Article 3 and Annex IB. See also Box 2.

The present article accepts that the Court's conclusion on the scope of the mutagenesis exemption in Article 3(1) *iuncto* point 1 of Annex IB is not inconsistent with the historical development of the Directive. At the same time this contribution claims that a further elaboration of the notion of a "long safety record", referred to in Recital 17, would be not only welcome but also necessary.

2. Possible wider implications of the ruling

The Court's ruling had been awaited with great anticipation because it was requested against the backdrop of a discussion on precisely which organisms developed through so-called New Breeding Techniques (hereafter NBTs) fall under the existing definition of GMOs. Before looking at the judgment's wider implications, the contours of the NBTs debate will first be sketched.

¹⁶ Somsen, *supra*, note 7, p 709.

a. GMOs and NBTs

The discussion whether and to what extent NBTs result in GMOs (or a similar regulatory term) has been held since the mid-2000s in many jurisdictions around the world. The term NBTs is used in these discussions as an umbrella term that captures a range of different techniques deployed in plant research and breeding, such as: genome editing, RNA-directed DNA methylation, grafting on GM rootstock, reverse breeding, transient expression, Agro-infiltration and cis-genesis.¹⁷

The reason these types of techniques are the subject of discussion in the regulatory context is that they may result in organisms with genetic changes that could also be obtained by conventional breeding, that do not contain foreign DNA, that only temporarily possess new genetic traits, or that are otherwise indistinguishable from conventionally produced organisms. From a regulatory point of view, this raises the question of whether organisms developed through NBTs come within the scope of the biosafety regulations and if so, how those regulations could be effectively enforced, given that the resulting organisms are often indistinguishable from naturally occurring or conventionally produced organisms.

The current global discussion focuses primarily on one specific type of NBT, often referred to as “genome editing” or “gene editing”, a tool that allows targeted high precision alterations in an organism’s genome.¹⁸ The alterations brought about by genome editing can range from small base pair changes or deletions that also occur naturally to the formation of entirely new functional genes.¹⁹ See also Box 3.

Over the past decade, discussions about the regulatory status of organisms developed through genome editing have in many jurisdictions resulted in the conclusion that it can only be established on a case-by-case basis whether an organism developed through genome editing falls under the relevant regulatory definitions, such as the regulatory definitions of GMOs.²⁰ In some countries, such as Brazil and Argentina,²¹ that assessment is made by the authorities, while in other countries the developers can make an initial determination of the status of their products and act accordingly, though there are mechanisms in place to seek the views of the authorities.²²

¹⁷ For an overview of NBTs, see for example the report of the High Level Group of Scientific Advisors, New Techniques in Agricultural Biotechnology (2017) <ec.europa.eu/research/sam/pdf/topics/explanatory_note_new_techniques_agricultural_biotechnology.pdf#view=fit&pagemode=none>, and M Lusser and others, *New Plant Breeding Techniques: State-of-the-Art and Prospects for Commercial Development*. (Publications Office 2011): Annex 16: “Task force on detecting and identifying crops produced with the new plant breeding techniques – Report” <dx.publications.europa.eu/10.2791/60346>.

¹⁸ In many papers on the subject, the terms genome editing and gene editing are used interchangeably. This article uses the term “genome editing”.

¹⁹ Genome editing is clarified in the explanatory note of the European Commission’s High Level Group of Scientific Advisors “New Techniques in Agricultural Biotechnology”: “The purpose in doing so is to enable the insertion of random (SDN1), or non-random (SDN2) mutations in precise locations, or to enable the insertion of large segments (such as genes) in precise locations (SDN3), see supra, note 17.

²⁰ D Eriksson et al, “A Comparison of the EU Regulatory Approach to Directed Mutagenesis with That of Other Jurisdictions, Consequences for International Trade and Potential Steps Forward” (2019) 222 *New Phytologist* 1673.

²¹ AI Whelan and MA Lema, “Regulatory Framework for Gene Editing and Other New Breeding Techniques (NBTs) in Argentina” (2015) 6 *GM Crops & Food* 253.

²² For example in the US, see the FAQ by the United States Department of Agriculture “USDA APHIS | ‘Am I Regulated’ Process” <www.aphis.usda.gov/aphis/ourfocus/biotechnology/am-i-regulated>.

Box 3. Technical context – types of genome editing²³

There are various types of genome editing. The techniques that are currently most widely used are:

- *Oligonucleotide-directed mutagenesis (ODM) genome editing*, which makes use of synthetic oligonucleotides that share homology with a target sequence(s). Oligonucleotides “target” the homologous sequence in the genome and create a “mismatch” at the base pair that is to be modified. This mismatch is recognised by the cell’s own DNA repair machinery and corrected by the cell itself introducing the repaired nucleotide sequence. After the DNA alteration, the oligonucleotide is degraded.
- *Site-directed nuclease (SDN) genome editing*, which involves DNA-cutting enzymes (nucleases) that cut the DNA at a predetermined location. After the cut in the DNA is made, the cell’s own DNA repair mechanism recognises the break and repairs the damage, using one of two pathways:
 - *non-homologous end-joining (NHEJ)*: the cut DNA is re-joined, but in the process a few base pairs are “eaten away” or added, resulting in random small deletions or additions of nucleotides at the cut site.
 - *homology-directed repair (HDR)*: a donor DNA that carries the desired change and has homology with the target site is used to introduce this change at the cut site. This can replace an existing DNA sequence or add a new sequence at the target site.

Unlike the progress in other parts of the world in clarifying these regulatory questions, the discussion in the EU has not yet resulted in clear guidance as to which organisms developed through NBTs fall under the EU GMO definition. Formalised discussions started in the EU in 2007 with the establishment by the European Commission of a Working Group on New Breeding Techniques, consisting of legal and technical experts nominated by the Member States. A key topic in these discussions concerned the definition of GMO in the Directive, and in particular whether the phrase “altered in a way that does not occur naturally by mating and/or natural recombination” refers to the technique used, to the resulting novel genetic combination,²⁴ or to both.²⁵

Despite the fact that opinions have been produced by various expert bodies such as the Working Group on New Breeding Techniques, the EU’s Joint Research Centre,

²³ For a further overview and more detail on genome editing, see for example: DD Songstad et al, “Genome Editing of Plants” (2017) 36 *Critical Reviews in Plant Sciences* 1, and: D Jaganathan et al, “CRISPR for Crop Improvement: An Update Review” (2018) 9 *Frontiers in Plant Science* <[www.frontiersin.org/article/10.3389/fpls.2018.00985/full](https://doi.org/10.3389/fpls.2018.00985/full)>.

²⁴ In this article the terms “new” and “novel” are used interchangeably.

²⁵ This discussion has often been referred to as the “process versus product” debate. See below for more detailed reflections.

the European Food Safety Authority and the High Level Group of Scientific Advisors,²⁶ the European Commission has not yet provided an interpretative opinion as to which organisms developed through NBTs fall under the EU definition of GMO. Since 2016, the Commission has indicated on multiple occasions that it would wait for the Court's *Confédération paysanne* ruling.

b. Possible wider implications of the ruling on the legal status of organisms developed through NBTs

As noted above, the Court confirmed that techniques of mutagenesis constitute GMOs in the sense of the Directive, and that organisms obtained by means of new techniques/methods of mutagenesis are not excluded from the Directive. Although the ruling does not clarify the term “new techniques/methods of mutagenesis”, paragraph 47 of the ruling refers to “techniques/methods of directed mutagenesis involving the use of genetic engineering”. To understand the implications of this finding of the Court, we need to know what is meant by “genetic engineering” and what constitutes “techniques/methods of mutagenesis”.

Crucially, “genetic engineering” is not a legal term used in the Directive,²⁷ nor is it defined in the ruling. The term “techniques/methods of mutagenesis” is mentioned in the Directive, but is not elaborated either in the Directive or in the ruling of the Court. To understand the latter's true scope then, it is essential to know what these terms could mean.

In this regard we do know that:

- Techniques/methods of mutagenesis involve the formation of changes within the genome of an organism, through mechanisms such as the cell's DNA repair mechanism. See also Box 4 on mutagenesis.
- When organisms developed through techniques/methods of mutagenesis constitute GMOs under the Directive, this means that the resulting organisms must comply with the substantive definition of GMOs in Article 2, ie they are “altered in a way that does not occur naturally by mating and/or natural recombination”. See section III for a detailed discussion on this term.

²⁶ Currently known as the Scientific Advisory Mechanism (SAM).

²⁷ In this regard it may also be noted that the term “genetic engineering” has a particular legal connotation in biosafety legislation outside the EU, such as the regulations under the auspices of the US Department of Agriculture. In EU law, the term “genetic engineering” is used in the Directive 98/44/EC on the protection of biotechnological inventions, yet it is a generic term construed for the purposes of conveying patent protection. As Directive 98/44/EC does not contain any explanations of the term, it cannot serve as a means for making any distinctions between “genetic engineering” and “genetic modification” for the purposes of this article.

The use of site-directed techniques such as ODM and SDN can have many different results, ranging from single base pair changes, additions or deletions to the template-mediated formation of a new gene. Single base pair changes and deletions do occur naturally and, in accordance with the GMO definition, cannot therefore result in a GMO. On the other hand, the formation of a functional gene that does not occur in the organism's genome is something that goes beyond what occurs naturally by mating and/or natural recombination, and therefore results in a GMO. Likewise, multiple single base pair changes may or may not result in something that goes beyond what occurs naturally by mating and/or natural recombination. In short: not every mutation is the result of a technique of mutagenesis in the sense of the Directive.²⁸

The question what kind of genetic alterations result from techniques of mutagenesis in the sense of the Directive can therefore only be assessed on a case-by-case basis. The ruling does not provide explicit guidance in this respect.^{29,30}

Further clarification by the EU institutions or by the Court will therefore be important. The study requested by the Council in October 2019 offers a good opportunity in this respect.

²⁸ In a stakeholder consultation that the European Commission organised in the context of a study on the status under Union law of novel genomic techniques as requested by the Council of the EU, novel genomic techniques are defined as “techniques, which are capable to alter the genetic material of an organism and which have emerged or have been developed since 2001”. After giving some examples, such as CRISPR, the Commission writes: “These techniques can lead to mutagenesis and some of them also to cisgenesis, intragenesis or transgenesis”. The term “can” suggests that the Commission – too – is of the view that not every application of genome editing techniques results by definition in mutagenesis in the sense of the Directive.

²⁹ While the ruling did not explicitly indicate what kind of genetic alterations constitute mutagenesis, some considerations in the ruling might shed some light on the Court's general thinking in this. For example, in para 48 of the ruling the Court states that “It thus follows from the material before the Court, first, that the direct modification of the genetic material of an organism through mutagenesis makes it possible to obtain the same effects as the introduction of a foreign gene into that organism ...”. Further, the Court refers in paras 48 and 55 to “transgenesis” and “transgenesis techniques”. It would be important to have clarified whether the use of the terms “foreign gene”, “transgenesis” and “transgenesis techniques” suggests that the kind of alterations that originate from mutagenesis are of the magnitude of introducing a gene from an unrelated species. As noted above, there have been multiple statements and papers suggesting that the ruling means that all genome-edited organisms fall under the GMO definition. In only very few cases were these suggestions accompanied by an analysis of the ruling, and in cases where substantiation was provided, it was usually very brief. As an example, we highlight one particular type of argument that was used on several occasions: the fact that the ruling references ODM and SDN mean that all genome edited organisms constitute GMOs. The authors believe that such argumentation does not hold. The reference to ODM and SDN does not stand by itself but is given in connection with mutagenesis. As detailed above, one therefore needs to know what constitutes “techniques/methods of mutagenesis”. In other words: the Court did not state that its mentioning in the ruling of undefined terms that do not appear in the Directive means that the substantive definition in Art 2(2) no longer applies.

³⁰ In February 2020, the French Conseil d'État applied the ruling of the Court, and, on this point, used virtually the exactly same language of the Court's ruling and did not touch on the more general question to what extent genome edited organisms are by necessity always GMOs. See Conseil d'État, 7 February 2020, Organismes obtenus par mutagenèse, Case No 388649, point 6.

Box 4. Technical context – Generating genetic variation

Broadly speaking there are two ways in which new genetic characteristics can be obtained in an organism:

1. Introducing genes from another organism into the genome of an organism. This can be done through a variety of approaches including conventional crossing or mating (whereby tens of thousands of genes are exchanged), cell fusion and recombinant DNA techniques whereby one or a few genes are introduced;
2. Generating genetic variation within existing genomes through mechanisms such as the cell's DNA repair mechanism. The DNA repair mechanism repairs single- or double-strand breaks, or mismatches, in the DNA. These breaks may occur naturally or be induced. Here it should be noted that also, under natural circumstances, DNA in the cell gets damaged regularly, which can result in DNA breaks of various kinds. Also a variation of endogenous factors in the cells will result in mutations. DNA damage is repaired by the natural repair mechanisms of the cell. The repair of DNA breaks occasionally results in random mutations, because the DNA repair process is not perfect and a few base pairs can be randomly removed or added, resulting in random small deletions or additions of nucleotides at the lesion site. Exposing cells to radiation or mutagenic chemicals can result in large numbers (sometimes many thousands) of randomly located DNA breaks or changes that are repaired by the natural DNA repair mechanism and can result in the simultaneous occurrence of large numbers of random mutations.³¹ Genome editing techniques, such as CRISPR, also result in increased variation within existing genomes. See also Box 3 on genome editing.

3. Concluding remarks on the Court's ruling

The confirmation of the Court that organisms obtained by means of techniques/methods of mutagenesis constitute GMOs under Directive 2001/18 follows directly from the text of the Directive and is consistent with its negotiation history.

The fact that organisms obtained using the techniques/methods of mutagenesis constitute GMOs under the Directive means that the resulting organisms must comply with the GMO definition, ie the genetic material of the resulting organisms has been altered in a way that does not occur naturally by mating and/or natural recombination.

The conclusion that organisms obtained by means of techniques/methods of directed mutagenesis were not intended to be excluded from the scope of the Directive is not inconsistent with the negotiation history of the Directive.

However, whether an organism falls under the description of being “obtained by means of techniques/methods of directed mutagenesis” must, in order to comply with the Directive, depend on whether the genetic material of the resulting organisms has been altered in a way that does not occur naturally by mating and/or natural recombination.

As a result, the ruling does not allow for categorical statements on the legal status of organisms developed through genome editing. Not every application of genome editing

³¹ See eg N Brown, “Mutagenesis – PlantBreeding” <plantbreeding.coe.uga.edu/index.php?title=16._Mutagenesis>; MC Negrito, “Double-Strand DNA Breaks | Learn Science at Scitable” <www.nature.com/scitable/topicpage/repairing-double-strand-dna-breaks-14432332/>. This technique of induced mutation has been used for almost a century and has resulted in over 3,000 varieties of food crops. See: “MVD – Home” <mvd.iaea.org/#!Home>.

results in mutagenesis in the sense of the Directive since some applications result in alterations that *do* occur naturally. What kind of genetic alterations result from a technique of mutagenesis in the sense of the Directive can therefore only be assessed on a case-by-case basis. The ruling does not provide explicit guidance in this respect, and further clarification by the EU institutions or by the Court will be important.

III. THE LEGAL STATUS OF ORGANISMS DEVELOPED THROUGH NOVEL GENOMIC TECHNIQUES

In the final section of this article we will try to identify a way forward in relation to the legal status of organisms developed through novel genomic techniques (hereafter: “NGTs”) by providing a detailed analysis of the GMO definition of the Directive.

1. The need for clarification

In October 2019 the Council requested the European Commission to submit, in light of the Court’s ruling, a study regarding the status of NGTs under Union Law.³² The study should be available no later than 30 April 2021. The Council further requested the Commission to submit a proposal, if appropriate in view of the outcomes of the study, or otherwise to inform the Council on other measures required as a follow-up to the study. It should be noted that the Council request refers to “novel genomic techniques”, which is not a term that features in the Directive, and which might – therefore – allow for a broad and unhindered discussion of the topic.³³

As part of the preparation of the requested study, the Commission early on in 2020 initiated stakeholder consultations³⁴ on NGTs. For the purpose of the study, the Commission provides the following definition of NGTs: “techniques, which are capable to alter the genetic material of an organism and which have emerged or have been developed since 2001”.³⁵ According to the Commission:

[e]xamples of techniques include: 1) Genome editing techniques such as CRISPR, TALEN, Zinc-finger nucleases, mega nucleases techniques, prime editing etc. These techniques can lead to mutagenesis and some of them also to cisgenesis, intragenesis or transgenesis. 2) Mutagenesis techniques such as oligonucleotide-directed mutagenesis (ODM). 3) Epigenetic techniques such RdDM.³⁶

The stakeholder consultation focused on the technical status and potential impacts of NGTs.

Bearing in mind the request of the Council, it is to be expected that after consideration of the technical status of NGTs, the Commission will address the legal status of organisms

³² Council Decision 2019/1904, *supra*, note 8.

³³ It should also be noted that the ruling made reference only to some forms of directed mutagenesis and not to other NBTs.

³⁴ See J Binns, *supra*, note 9.

³⁵ *ibid.*

³⁶ *ibid.*

developed through NGTs. It is on the latter point that the next section will make suggestions for clarification.

2. Going back to the GMO definition in Directive 2001/18

a. “Process vs product”

As described above, a key element in the discussions on the GMO definition is whether the phrase “altered in a way that does not occur naturally by mating and/or natural recombination” refers to the resulting organism, to the technique used or to both.

Following the Court’s standard methods of interpretation, the sections below analyse the GMO definition, in particular regarding the above point, by considering the *wording*, the *general scheme* and the *spirit* of the EU GMO Directive.³⁷

b. The wording of the EU GMO definition.

Article 2(2) defines a GMO as:

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:

- genetic modification occurs at least through the use of the techniques listed in Annex IA, part 1;
- the techniques listed in Annex IA, part 2, are not considered to result in genetic modification[.]”³⁸

In light of this definition, a number of observations are in place. First, a literal reading of the term “altered” in Article 2(2) suggests that something has been changed or made different. This refers to a change in a state or a result. Second, Article 2 and the heading of Annex I refer to “techniques”. This multiple reference to techniques suggests that the technique relied upon must also be considered. Third, Annex IA, part 1 refers in its point 1 to:

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.

Both the technique and the resulting alterations to the genetic material are thus explicitly referred to. Had the legislator intended that the mere use of certain techniques would result in a GMO, then it would not have added the qualifications “new combinations of genetic material” and “in which they do not naturally occur but in which they are

³⁷ J Bengoetxea, *The Legal Reasoning of the European Court of Justice: Towards a European Jurisprudence* (Oxford, Clarendon Press; Oxford University Press 1993).

³⁸ Annex IA of the Directive is appended to this article together with Art 2.

capable of continued propagation”. Also, the term “incorporation” underlines the focus on the genetic alteration that results from the technique relied upon. Fourth, Annex IA, part 1 refers in point 2 to “techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation”. Again, both technique and the resulting alterations to the genetic material are thus explicitly referred to. Fifth and lastly, Annex IA, part 1 refers in its point 3 to “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”. Here too both the technique and the resulting new combinations to the genetic material are referred to. The qualification “live” also confirms that the resulting organism needs to be taken into account.

Taken together, a literal reading of Article 2 and Annex I suggests that for an organism to be a GMO, both the technique and the resulting alterations to the genetic material should be taken into account. This is also confirmed by the explanatory memorandum to the proposal for Directive 90/220, which elaborates on the meaning and purpose of Annex I Part 1: “this annex is intended to provide, through a periodical update, a clarification of what techniques *can* make an organism genetically modified within the meaning of this Directive ...”.³⁹ This also suggests that the use of a certain technique does not in itself constitute a GMO.⁴⁰

c. The general scheme of the EU GMO legislation

With respect to the general scheme of the EU GMO legislation we consider the historical and the broader regulatory context.

In terms of historical context, the negotiations for the Directive and its predecessor Directive 90/220 built on the 1982 Council Recommendation 82/472,⁴¹ which defines “Work involving recombinant DNA” as “the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation”. As noted above, this phrasing suggests that the level of genetic novelty of the resulting organism is a key component of what constitutes a GMO.

³⁹ European Commission, Explanatory memorandum to proposals for Council Directives on the contained use of genetically modified micro-organisms and on the deliberate release in the environment of genetically modified organisms, COM (88) 6397 final (not published), p 34 (emphasis added).

⁴⁰ Paragraph 28 of the 2018 CJEU ruling states: “Account being taken of the information provided by the referring court, it must be noted, first, that the mutations brought about by techniques/methods of mutagenesis such as those at issue in the main proceedings, the implementation of which is intended to produce herbicide-resistant varieties of plant species, constitute alterations made to the genetic material of an organism, for the purposes of Article 2(2) of Directive 2001/18”. The use of “constitute” in relation to Art 2 also suggests, as in the above interpretation, that for an organism to be considered a GMO, consideration should be given to the type of resulting alterations to the genetic material.

⁴¹ Recommendation (EEC) 82/472 concerning the registration of work involving recombinant deoxyribonucleic acid (DNA) [1982] OJ L213/15.

Regarding the broader regulatory context, it should be observed that the EU and its Member States are Parties to the Cartagena Protocol on Biosafety (CPB), which defines in Article 3 the key regulatory term “living modified organism” as follows:

Any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology, whereby “Modern biotechnology” means the application of:

- a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or
- b. fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection.

This definition of the CPB makes explicit reference to the technique used (i.e. “through the use of modern biotechnology”) and to the genetic novelty of the resulting organisms (“possesses a novel combination of genetic material”).⁴² The level of novelty is clarified by the phrase “overcome natural physiological reproductive or recombination barriers”.

As Article 9.3 of the CPB states: “The domestic regulatory framework referred to in paragraph 2 (c) above, shall be consistent with this Protocol”.⁴³ In the explanatory memorandum to the proposal for Regulation 1946/2003 on the implementation of the CPB,⁴⁴ the European Commission declared that “[t]he definition of an LMO under the Protocol is largely consistent with the definition of a Genetically Modified Organism (GMO) under Directive 2001/18”.⁴⁵ “Largely consistent” suggests an extensive compatibility between the two definitions and their core requirements. Further, the explanatory memorandum noted, with regard to the differences between the definitions, that “this is not likely to impinge on operational aspects of the legislation”. This also suggests that in clarifying what constitutes a “new combination of genetic material”, an important factor would be whether that new combination overcomes natural physiological reproductive or recombination barriers.

d. The spirit of the EU GMO legislation

In assessing the “spirit” of legislation, the Court typically considers three types of criteria, these being teleological, functional and consequentialist in nature.

⁴² The term “possesses” refers to the fact that a certain novel genetic combination must still be present in the organism for it to be an LMO.

⁴³ Further, also under EU law itself (Art 216(2) TFEU – Consolidated version of the Treaty on the Functioning of the European Union [2012] OJ C326/1) international agreements concluded by the EU are binding on its institutions, meaning ordinary secondary EU legislation needs to conform to (and be interpreted in light of) such agreements. See eg Case C-344/04, *International Air Transport Association and European Low Fares Airline Association v Department of Transport*, ECLI:EU:C:2006:10, para 35.

⁴⁴ Regulation of the European Parliament and the Council (EC) 1946/2003, on transboundary movements of genetically modified organisms [2003] OJ L 287/1.

⁴⁵ European Commission, Explanatory memorandum to the proposal for a Regulation of the European Parliament and of the Council on the transboundary movement of genetically modified organisms, COM (2002) 0085 final.

In terms of a teleological and a functional interpretation of the definition, it is important to consider that an essential component of biosafety legislation is scientifically sound risk assessment. The starting point in risk assessment is to identify whether the genetic modification results in new characteristics that may have adverse effects. As part of that process, the new characteristics of the GMO are compared with non-modified counterparts. This focus on new characteristics confirms that novelty is a key element of the definition. If the definition of a GMO were interpreted as the mere use of a certain technique resulting in a GMO, and also if the resulting organism were indistinguishable from conventionally produced organisms, then this would make the risk assessment illusory. Finally, under a consequentialist interpretation, an essential component of any regulation is its enforceability, which in the case of GMOs is based on enforcement authorities being able to detect and distinguish organisms subject to regulation from organisms that are not subject to regulation. If the definition of a GMO were interpreted as the mere use of a certain technique resulting in a GMO even if the resulting organism could not be distinguished from conventionally produced organisms, then this would make it, in those cases, impossible for regulatory authorities to independently verify compliance with the regulation, ie to be able to detect and identify (i.e. distinguish) the organisms.⁴⁶

In conclusion: considering the wording, general scheme and spirit of the EU GMO legislation, we thus argue that for an organism to be a GMO in the meaning of the Directive, both the technique used and the level of novelty of the resulting genetic alterations must be considered.

Finally, building on this conclusion, the next question is what level of genetic alteration would be considered as “not occur[ring] naturally by mating and/or natural recombination”. The study requested by the Council offers a good opportunity to provide further clarity.

In that respect, we offer the following observations:

- The process of clarifying terms like the above is often served by describing cases at both ends of the spectrum, ie cases that would clearly fall under the description “does not occur naturally by mating and/or natural recombination” and cases that would not fall under that description. For example, the incorporation of structural genes originating from an insect into a plant is a case of “does not occur naturally”. Conversely, the incorporation in the genome of an apple tree of a gene from a sexually compatible apple tree, is a case of “occurring naturally”. Likewise, small point mutations in every organism occur frequently in nature,

⁴⁶ Regulating organisms that cannot be distinguished from conventionally developed organisms poses challenges in terms of enforcement as described above and can also have a significant impact on trade. The latter would be the case if such organisms fall under the GMO regulations of some countries while they do not fall under such regulations of other countries. This issue has become particularly urgent now that the first gene-edited crops are entering the market in Northern America (eg soybean and canola). See also European Network of GMO Laboratories (ENGL), *JRC Technical Report – Detection, Interpretation and Reporting on the Presence of Authorised and Unauthorised Genetically Modified Materials (Working Group Report)* (2017) <gmo-crl.jrc.ec.europa.eu/doc/JRC116289-GE-report-ENGL.pdf>.

and are therefore “occurring naturally”. The challenge will be addressing the “grey area” between the two ends of the spectrum.⁴⁷

- Over the last decades, scientific evidence has shown that what was thought 20 years ago not to occur naturally, now appears to happen frequently in nature in organisms. For example, research has shown widespread horizontal gene transfer, such as through *Agrobacterium*^{48,49,50} and transposable elements via vectors.⁵¹

IV. CONCLUSIONS AND RECOMMENDATIONS

While the Court’s ruling on mutagenesis in *Confédération paysanne* sheds light on the Court’s general thinking in relation to techniques of mutagenesis, the ruling does not provide clarification as to when an organism falls under the description of “obtained by means of new techniques/methods of mutagenesis”, nor was the Court asked to do so.

For a variety of scientific and societal reasons, it is imperative that the regulatory status of organisms developed through novel genomic techniques is clarified as a matter of urgency.

The 2019 Council request to the European Commission to submit a study regarding the status of novel genomic techniques under Union Law offers a good opportunity to provide such clarification.

To contribute to the debate on the legal status of organisms developed through novel genomic techniques, this article analyses the EU GMO definition, concluding that both the technique used and the level of novelty of the resulting genetic alterations must be considered in assessing whether an organism is a GMO under Union Law.

The 2019 Council request further asked for a proposal, if appropriate in view of the outcomes of the study, or otherwise to inform the Council on other measures required as a follow-up to the study.

In this respect, there are various options available, such as:

- a published interpretation by one or more EU institutions,
- a further elaboration by the Court on the ruling on mutagenesis in *Confédération paysanne*,
- a change of the GMO definition and/or the annexes.

⁴⁷ See eg R Custers et al, “Genetic Alterations That Do or Do Not Occur Naturally; Consequences for Genome Edited Organisms in the Context of Regulatory Oversight” (2019) 6 *Frontiers in Bioengineering and Biotechnology* <www.frontiersin.org/article/10.3389/fbioe.2018.00213/full>.

⁴⁸ TV Matveeva and L Otten, “Widespread Occurrence of Natural Genetic Transformation of Plants by *Agrobacterium*” (2019) 101 *Plant Molecular Biology* 415.

⁴⁹ DG Quispe-Huamanquispe et al, “Horizontal Gene Transfer Contributes to Plant Evolution: The Case of *Agrobacterium* T-DNAs” (2017) 8 *Frontiers in Plant Science* <journal.frontiersin.org/article/10.3389/fpls.2017.02015/full>.

⁵⁰ K Chen and L Otten, “Natural *Agrobacterium* Transformants: Recent Results and Some Theoretical Considerations” (2017) 8 *Frontiers in Plant Science* <journal.frontiersin.org/article/10.3389/fpls.2017.01600/full>.

⁵¹ X Diao et al, “Horizontal Transfer of a Plant Transposon” (2005) 4 *PLoS Biology* e5. P Vallenback et al, “Origin and Timing of the Horizontal Transfer of a PgiC Gene from *Poa* to *Festuca Ovina*” (2008) 46 *Molecular Phylogenetics and Evolution* 890.

An interpretation of the legislation by EU institutions is possible and results in a non-binding document, eg a guidance document from the European Commission, a resolution by the European Parliament, or a Recommendation by the Council of Ministers.⁵² Obviously this interpretation should respect the Court's clarification in *Confédération paysanne* but as we have attempted to show above, the Court in that case only clarified the scope of the exemption, while the interpretative guidance of the EU institutions would focus on the scope of the GMO definition.⁵³

Further elaboration by the Court is also possible: if national courts entertain doubts on the meaning or scope of a preliminary ruling, they can always ask for further elaboration by referring new questions to the Court.⁵⁴ The highest national courts are even under an obligation to refer such questions, in so far as they arise, to the Court.⁵⁵ This applies to the national court that originally referred the case to the Court of Justice, as well as to all other national courts of all the EU Member States since they are also expected to follow the ECJ's ruling.⁵⁶ Although the Court can answer such question in a "minimalistic" fashion, it should be noted that in the preliminary ruling procedure it is not uncommon for the Court of Justice to interpret additional or different provisions of EU law other than those indicated by the referring national court. The Court will typically do so in order to give a useful answer, allowing the national court to decide the case before it.^{57,58} Since all Member States and the EU institutions are entitled to submit observations to the Court in the course of such proceedings, they would indeed be well advised to make use of this option.

Changing the GMO definition or the annexes is also possible and means changing the Directive. Any such changes should be very carefully prepared in consultation with all relevant stakeholders, while avoiding the problem that, after any changes take effect, scientific developments demand further changes. Careful preparation is particularly important, because the process of changing the Directive may take many years, in part because once a formal amendment to the Directive is proposed, other changes in the procedure can be put forward.

While we believe that the uncertainty around the status of organisms developed through NBTs can be addressed through further elaboration by EU institutions or by the Court, we also believe that there is an urgent need for a thorough, comprehensive

⁵² For example, Council Recommendation (EEC) 82/472 supra, note 41.

⁵³ Since such interpretative guidance would be non-binding, it would also be impossible to challenge its legality under Art 263 TFEU. It is only exceptionally that recommendations or opinions (in the sense of Art 288 TFEU) can be challenged and for this the applicant has to show that the guidance does not in fact constitute a genuine recommendation. See Case C-16/16 P, *Belgium v Commission*, ECLI:EU:C:2018:79. On the other hand, the Court can be asked to interpret such interpretative guidance pursuant to Art 267 TFEU, see eg Case C-322/88, *Grimaldi*, ECLI:EU:C:1989:646.

⁵⁴ Thus national Courts can even refer preliminary questions to the Court asking about the interpretation of an earlier preliminary ruling, see Case 69/85, *Wünsche*, ECLI:EU:C:1986:104, para 15.

⁵⁵ See Art 267 TFEU.

⁵⁶ See ia Case C-300/17, *Hochtief*, ECLI:EU:C:2018:635, para 55.

⁵⁷ K Lenaerts et al, *EU Procedural Law* (first edition, Oxford, Oxford University Press 2014), pp 235–237.

⁵⁸ Some Member States have already raised some questions in the wake of the Court ruling. For example, in a letter to the European Commission in October 2018, Sweden pointed out that it is difficult to understand the risk-based arguments used in the Court ruling while asking if it is not reasonable to presume that molecular changes that are exactly the same would carry the same risk, no matter how they were produced. Swedish Board of Agriculture (2018). Follow-up from PAFF-meeting on 11 September 2018. Dnr 5.1.21-124/18. Letter to the European Commission on 1 October 2018, available on request from jordbruksverket@jordbruksverket.se.

review of the EU regulatory frameworks for GMOs that takes into account advances in knowledge and experience as well as consistency with international law.

V. APPENDIX: ARTICLE 2(2), ANNEX IA AND ANNEX IB TO DIRECTIVE 2001/18

1. Article 2(2)

“[G]enetically 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:

- genetic modification occurs at least through the use of the techniques listed in Annex IA, part 1;
- the techniques listed in Annex IA, part 2, are not considered to result in genetic modification[.]

2. Annex IA: Techniques referred to in Article 2(2)

a. Part 1

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.

b. Part 2

Techniques referred to in Article 2(2)(b) which are not considered to result in genetic modification, on condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms made by techniques/methods other than those excluded by Annex IB:

- (1) in vitro fertilisation,

- (2) natural processes such as: conjugation, transduction, transformation,
- (3) polyploidy induction.

3. Annex IB – Techniques referred to in Article 3

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.