On July 25th 2018, the Court of Justice of the European Union (CJEU) decided on the legal classification of organisms developed by mutagenesis.

The decision can be found here: https://bit.ly/2v0KMAo

The opinion below has to be considered obsolete and will remain online for purposes of documentation only.

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Bundesamt für Verbraucherschutz und Lebensmittelsicherheit

Opinion on the legal classification of New Plant Breeding Techniques, in particular ODM and CRISPR-Cas9

A. Introduction

Currently, discussion is ongoing throughout the EU as to what extent organisms developed with the help of so-called “new plant breeding techniques” – in particular the techniques of oligonucleotide-directed mutagenesis (ODM) and CRISPR-Cas9 – fall under the scope of application of Directive 2001/18/EC (hereinafter referred to as the Directive[1]). A common feature of these techniques – provided one regards only the induction of point mutations, as is the case in the following – is that the genetic modifications which they cause could also result from conventional breeding techniques[2] or natural processes.

The legal opinions of Prof. Dr. Ludwig Krämer[3] and Prof. Dr. Dr. Tade Matthias Spranger[4] come to the conclusion that these techniques fall within the scope of the Directive.

In the opinion of BVL, this conclusion is not correct for the following reasons:

Organisms which exhibit point mutations generated through the use of ODM and CRISPR-Cas9 techniques do not constitute genetically modified organisms (GMOs) within the meaning of the Directive. The term GMO presupposes that the organism’s genetic material has been altered in a way that does not occur naturally, and that this modification cannot be achieved by mating and/or natural recombination. In this respect, Article 2(2) refers to the process by which the genetic modification is induced as well as to the genetic modification that occurs in the organism as a result of that process (for details please refer to section B).

Even if said organisms were regarded as GMOs anyways, the techniques used would fall under the exemption rule of Article 3(1) in conjunction with Annex I B, No. 1, (for details please refer to section C).

BVL therefore concludes that the following organisms do not fall under the scope of the Directive:

- Organisms generated by conventional breeding methods, even if they exhibit new characteristics (e.g. Clearfield oilseed rape).
- Organisms generated using (new) genetic modification techniques where the genetic modification could also be produced by conventional breeding methods (e.g. Cibus oilseed rape).
- Organisms generated by genetic modification techniques which are excluded from the scope of the Directive under the terms of Annex I B (e.g. products created using mutagenesis methods).

Therefore, BVL also maintains its assessment decision in the case of Cibus oilseed rape.

[1] Unless otherwise stated, all provisions mentioned in the text, including the recitals, are those of Directive 2001/18/EC.

[2] In the case of conventional breeding techniques, genetic modifications are also actively generated by means of physical and chemical processes. Actively generated mutations as well as those which occur spontaneously through natural processes are selected and propagated by breeders with respect to the desired product.

[3] Krämer, Legal questions concerning new methods for changing the genetic conditions in plants, September 2015.

[4] Spranger, Legal Analysis of the applicability of Directive 2001/18/EC on genome editing technologies, October 2015.

B. Definition of the term GMO within the meaning of Article 2(2)

In the opinion of BVL, ODM and CRISPR-Cas9 techniques used to induce point mutations[5] do not usually regularly give rise to GMOs in the sense of Article 2(2) for the following reasons:

Genetic engineering is understood as the possibility to make deliberate alterations to genetic material which could not be achieved by conventional breeding methods.[6]

Accordingly, under Article 2(2) 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".

Hence, when determining whether a GMO is produced or not, it is not just the process by which a genetic modification is induced that is of paramount importance. Rather, it is also important that the process gives rise to a genetic alteration in the organism which would not have been possible to induce through conventional breeding methods or natural processes. The definition is therefore not only related to the process but also to the product.

This follows not only from the wording (see I. and II. below) but also from the systematic (see III. below) and teleological interpretation of the Directive (see IV. below).

I. Wording of Article 2(2)

It cannot be derived from the wording of Article 2(2) that the GMO definition covers only the process by which the genetic modification is induced. Rather, it is also important that a product is created whose genetic material has been altered in a way that would not be possible by conventional breeding methods or natural processes. In this respect, the exclusion of natural events is directly related to the genetic material and not to the manner of modification.[7]

Referring to the phrase "in a way" as evidence of an exclusive reference to the process, on the other hand, is not convincing[8]. This "way" is not necessarily to be translated in the sense of the way of production; instead the phrase "in a way" has also to be understood in its adjective form.

The German phrase "*auf natürliche Weise*" (English: naturally) also suggests that the definition should be interpreted as being both process- and product-based in the sense of cumulative requirements. This becomes clear when the text is reviewed analytically.

There is no compelling reason to mention the word "mating" before "natural recombination". If one were to switch the two terms around, then a GMO would be "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 natural recombination and/or mating."

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[5] Serially repeated mutations, e.g. by means of ODM, involving the re-formation of a whole genome section are to be evaluated separately. However, on the one hand, this is a purely theoretical consideration at this point, because after each individual mutation process a new plant would have to be regenerated from a single cell in tissue culture. This cannot be repeated at will because such passaging results in the accumulation of somaclonal mutations which have a counterproductive effect on the plant breeding process. Tissue culture is a limiting factor here. On the other hand, repeated mutagenisis was not the case for the Cibus oilseed rape to which the BVL assessment refers.

[6] *Cf.* German Federal Constitutional Court judgement of 24 November 2010, BVerfG, 1 BvF 2/05, marginal number 2.

[7] See also Ostertag, GVO-Spuren und Gentechnikrecht, 2006, p. 160.

[8] *Cf.* in this respect Krämer, *ob. cit.*, marginal number 8 and footnote 5: *"The Directive does not look at the final result of the process, the organism, but rather at the way in which this final result is obtained. […] The Directive applies, when an organism is 'altered in a way'. This describes the <u>way</u>, not the* <u>end result</u> *of the process of genetic modification".*

The resulting juxtaposition of the terms “naturally” and “natural recombination” makes it clear that the term “naturally” would be redundant if it referred only to the process, because “natural recombination” and “mating” are already “natural ways”. So, it would then be determined that the process would not be possible in a natural way through naturally occurring events. This does not make sense because natural events always take place in a natural way.

II. Additional argument based on the wording in Annex I A, Part 1

A further wording argument in favour of an approach that is not only process-based but also product-based can be found in Annex I, Part 1, No. 1, where mention is made of recombinant nucleic acid techniques “involving the formation of new combinations of genetic material” as well as in (3), which lists, *inter alia*, cell fusion techniques “where live cells with new combinations of heritable genetic material are formed.”[9] Here it becomes apparent that the techniques must always also lead to a specific result (formation of new combinations of genetic material).

III. Systematics of the regulation

In addition, both the regulatory concept of the Directive (see point 1. below) and the systematics of EU law (see point 2. below) provide arguments against defining a GMO solely on the basis of the process by which it is created.

1. Regulatory concept of the Directive

The regulatory concept of the Directive shows that, in addition to the application of a genetic engineering method, an unnatural recombinant event also has to be created. So, as a supplement to the abstract definition of a GMO in Article 2(2), a system of examples and counter-examples of methods used to modify genetic material is found in Annex I A, Part 1 and Part 2. The non-exhaustive list serves, *inter alia*, as a basis for deregulation by exempting certain methods from the scope of the Directive.[10] The conventional genetic engineering methods listed in Annex 1 A, Part 1 share the common feature that, in addition to the insertion of the genetic material into the host organism, they require that the gene combinations thus produced do not occur under natural conditions (“do not naturally occur”).

A corresponding provision can be found in § 3(3a)(a) of the German Genetic Engineering Act (GenTG). In the Second Act to amend the GenTG this norm was complemented by the clarification that the gene combination may not occur under natural conditions.[11] According to the statement of grounds provided by the competent Bundesrat committees, the motivation for the clarification was that there was some doubt among monitoring authorities as to “whether one is dealing with contained use activities according to GenTG if the genetic material of an organism is modified using genetic engineering methods, but the organisms resulting from the genetic modification could also occur by mating or natural recombination. […] *Decisive for the classification is the result of the genetic modification, not the method”*.[12]

Among scientists, this is interpreted as meaning that even when a technique within the meaning of Annex 1 A, Part 1 is used, a GMO does not result as long as the modification could

[9] See also Callebaut, New developments in modern biotechnology: A survey and analysis of the regulatory status of plants produced through New Breeding Techniques, Master thesis, Ghent 2015, p. 44 f.

[10] For more details on this topic see Ronellenfitsch, in: Eberbach/Lange/Ronellenfitsch, GenTR/BioMedR, 90th supplement, vol. 1, § 3 GenTG, marginal number 77; Ostertag, *ob. cit.*, p. 160 f.

[11] § 3 No. 3(2) GenTG in its old version contained the passage in only one of the three variants.

[12] See Bundesratsdrucksache 33/1/02 of 19 February 2002, p. 8.

also take place under natural conditions.[13] Modifications which could also occur under natural conditions are not captured by the law on genetic engineering.[14] After all, the specific nature of genetic engineering lies not in the working methods used but in the potential results of recombination.[15]

Thereby, the question of whether a modification also occurs under natural conditions is not to be determined individually in an individual-concrete way.[16] For even conventional methods of mutagenesis, which are unequivocally excluded from the Directive, are not subject to a specific requirement that the same change would occur through natural processes. In this respect, it is always a general-abstract consideration that takes place.[17]

2. Systematics of EU law

The definition of the term GMO given in the Cartagena Protocol can also serve as an aid to interpretation.

Article 3(g) of the Cartagena Protocol (international law) defines the term “living modified organism (LMO)” as “any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology”. This definition clearly captures both the end product (living organism with a novel combination of genetic material) and the process (use of modern biotechnology).

In 2002, the Council adopted a decision on the accession of the EC to the Cartagena Protocol (Council Decision 2002/628/EC). Therewith, in accordance with Article 300(7) TEC[18], the EC and its institutions were henceforth bound to the provisions of the Cartagena Protocol when enacting secondary legislation as well. With the creation of Regulation (EC) No. 1946/2003, the EC legislator aimed to fulfil its obligations under international law arising from its accession to the Protocol: According to Article 1 of that Regulation, the declared objective is “to ensure coherent implementation of the provisions of the [Cartagena] Protocol on behalf of the Community”. And for the definition of the central term GMO in Article 3(2) of Regulation (EC) No. 1946/2003, the EC legislator refers explicitly to the definition in Article 2(2)[19] in question here.

It follows that in EU law the GMO term must be interpreted in the light of the Cartagena Protocol. Hence, in the same way as the definition of the term LMO in the Cartagena Protocol, it refers to both the process and the product.

IV. Teleological interpretation

The protective purpose of the Directive also has to be considered in this context. Its aim is to avoid adverse effects on human health and the environment which might arise from the deliberate release or the placing on the market of GMOs (cf. Article 4). Thereby, the risk assessment refers at all times to potential hazards posed by the organism deliberately released into the environment or placed on the market. It is not the process itself that is considered dangerous; rather it is the product which results from that process that must be examined for its potentially harmful effects.

Practical considerations also support the opinion put forward here.

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[13] See Ostertag, *ob. cit.*, p. 161, with reference to Ronellenfitsch, *ob. cit.*, § 3 GenTG, marginal number 90.
[14] *Cf.* Ronellenfitsch, *ob. cit.*, § 3 GenTG, marginal number 90.
[15] *Ibid.,* marginal number 88.
[16] A different view is taken by Spranger, *ob. cit.*, p. 17, who notes that: “the ‘not natural appearance’ has not been assessed in a general-abstract, but in an individual-concrete way”.
[17] For a different view see Spranger, *ob. cit.,* p. 17 f.
[18] Now Article 216(2) TFEU.
[19] For details see Callebaut, *ob. cit.*, p. 48.

1. Let us assume that a point mutation is inserted into a plant via ODM. In the opinions of Krämer and Spranger the result would be a GMO. If, again via ODM, this mutation were to be corrected at the same site and the organism were thus restored to its initial state, then the organism now generated would be absolutely biologically identical to the parental organism. In the opinions of Krämer and Spranger, that organism would, however, also be considered a GMO and would have to undergo a rigorous assessment. It cannot be derived from the purpose of the Directive that two absolutely identical organisms are to be treated differently under the law.

2. Let us assume that a manufacturer alters a plant by introducing a point mutation using ODM and subsequently applies for authorisation to place it on the market, as would be required according to the legal opinion of Krämer and Spranger. Under European law, under Article 13(2) and Annex III B, Section D., No. 12, the manufacturer would be required to provide, among other things, information about the methods used to detect and identify the GMO along with the application.

In reality, however, this alleged GMO would not be distinguishable from a plant which had acquired the same point mutation naturally or by means of chemical- or radiation-induced mutagenesis (which according to Annex I B is indisputably excluded from the scope of the Directive). Therefore, such a GMO would not be distinguishable from organisms which do not fall under the scope of the Directive. Ultimately this means that it would be impossible to monitor, and its placing on the market would not be eligible for approval because the application dossier is incomplete. This outcome cannot have been the intention of the legislator. Apart from that, this would mean that the EU's so-called zero-tolerance rule for non-approved GMOs in seed could no longer be fully implemented. This, too, cannot have been the intention of the legislator.

Moreover, basic principles such as "zero-tolerance" or coexistence (for the latter see Article 26a(2)) couldn't be practically enforced any longer, when following a strict process-based approach: Companies in countries outside of the European Union have already started commercially growing plants with point mutations induced by NPBTs (e.g. Cibus herbicide resistant canola in the US[20]). If seed samples for breeding purposes contain such seeds (which is likely to happen accidentally as they are not specifically regulated in these countries), genetic modifications caused by genome editing techniques will eventually enter the gene pool of breeding lines produced inside the EU. The problem of lacking ability to distinguish between genome-edited plants and plants with natural mutations would of course also apply for provisions on labelling or national penal laws (for the latter see Article 45).

VI. Interim result

It follows from the foregoing that organisms which exhibit point mutations induced by means of ODM and CRISPR-Cas9 techniques do not constitute genetically modified organisms (GMOs) in the sense of the Directive.

With regard to the GMO characterisation, the use of a genetic modification method is not the sole determining factor. Another decisive factor is that the outcome of the process differs from alterations which can arise through natural processes. Therefore, it is not the means of alteration alone but the genetic alteration induced by that means which is decisive.[21] Accordingly, specific techniques cannot be considered separately from their concrete

[20] See http://www.cibus.com/products.php , accessed on 12 October 2016.

[21] See Ostertag, *ob. cit.*, p. 161.

application[22]. So, a decisive factor is whether the qualitative threshold of "unnatural alteration" is exceeded.[23] For it is undisputed that the new techniques can also be used to generate GMOs, provided they are applied in such a way that the alterations produced would not be achievable through conventional methods. However, this is not the case for the point mutations being considered here. This opinion is also shared by the New Techniques Working Group (NTWG). In its report, the NTWG likewise comes to the conclusion that the point mutations generated by ODM or ZFN (zinc finger nuclease techniques, comparable to CRISPR-Cas9) can also arise from other mutagenesis processes and cannot be distinguished from point mutations caused by these.[24]

C. Application of the exemption rule of Article 3 in conjunction with Annex I B, No. 1

Even if organisms, whose genome got point mutated by new plant breeding techniques were regarded as GMO, , the exemption rule of Article 3(1) in conjunction with Annex I B, No. 1 would apply. According to this provision, the Directive is not applicable to organisms in which genetic modification was generated by means of mutagenesis (see I. below) without the use of recombinant nucleic acid molecules (see II.).[25] In addition, recital 17 does not prevent application of the exemption (see III.).

I. Mutagenesis

Mutagenesis is generally understood as the alteration of genetic material through external influences.[26] The term "mutagenesis" is not defined in the Directive. In particular, it is not restricted to specific types of modification, so that new techniques which were unknown at the time of the adoption of the Directive can basically also fall under its scope. The new plant-breeding techniques being examined here also fall under its scope.[27] For, point mutations induced by means of ODM and similar site-specific nuclease techniques (e.g. the corresponding use of the CRISPR-Cas9 technique) cannot be differentiated from point mutations which have arisen as a result of natural or induced mutagenesis (e.g. through chemicals).[28]

II. No presence of recombinant nucleic acid molecules

Furthermore, the organisms according to Annex I B, No. 1 must be generated without the use of recombinant nucleic acid molecules.

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[22] For a different view see Spranger, *ob. cit.*, whose analysis considers new techniques in general and is not restricted to point mutations.
[23] See Ostertag, *ob. cit.*, p.161.
[24] New Techniques Working Group, Final Report, point 5.1.5 B.
[25] This can be derived from the English wording of the regulation: "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 […]." The German version means the same but as a result of its positive phrasing ("*vorausgesetzt, es werden nur solche* […] *verwendet, die* […]" (on the condition that only such […] are used which […]) can easily lead to the misunderstanding that the use of GMOs or recombinant nucleic acid molecules is always a precondition for mutagenesis. However, this is not the case.
[26] See Ronellenfitsch, ob. cit., § 3 GenTG, marginal number 101.
[27] This is also the opinion of the EFSA: See EFSA Response to Mandate M-2015-0183 ("Request for EFSA to provide technical assistance with regard to issues related to the legal analysis of new plant breeding techniques") Question 2, http://registerofquestions.efsa.europa.eu/roqFrontend/wicket/page?6-1.ILinkListener-mandateForm-documents-2-fileNameLnk,accessed on 4 November 2015.
[28] EFSA Response to Mandate M-2015-0183 ("Request for EFSA to provide technical assistance with regard to issues related to the legal analysis of new plant breeding techniques") Question 2, http://registerofquestions.efsa.europa.eu/roqFrontend/wicket/page?6-1.ILinkListener-mandateForm-documents-2-fileNameLnk, accessed on 4 November 2015.

1. ODM

The oligonucleotides, as components of the mutagen in the ODM technique are not recombinant nucleic acids in the sense of the Directive. Although the term "recombinant nucleic acids" is not defined in the Directive, the wording in Annex I A, Part 1, No. 1 implies that "recombinant nucleic acid techniques" must involve the formation of new combinations of genetic material. But the oligonucleotides used in the ODM technique, with the exception of one or a few nucleotides, are identical to the corresponding site in the genome of the treated plant cells and therefore do not represent new combinations in the sense of new arrangements of genomic sequences. The validity of this point of view can also be proven historically: In the scientific field, the term "recombinant nucleic acids" can be traced back to the work of biochemist Paul Berg, who generated the first recombinant nucleic acid molecules in his laboratory at Stanford University in California (USA)[29]. In simple terms, the recombinant DNA produced by Paul Berg consisted of two DNA molecules of different origin which had been cut out with an enzyme and subsequently joined together using another enzyme. One DNA fragment used in this process was derived from the genome of a virus, the second from the bacterium *Escherichia coli*. The result was a new combination of genetic material which could not be generated naturally. In the following year, Stanley Cohen and Herbert Boyer[30] produced the first genetically modified organisms by inserting recombinant DNA, which they had generated in the test tube by combining DNA fragments from two strains of bacteria, into bacteria in which the DNA was able to replicate.

This interpretation of the term "recombinant nucleic acid" is also expressed by the EFSA in its response to a request of the European Commission: "[…] a recombinant nucleic acid molecule can be defined as a molecule that is generated by joining two or more nucleic acid molecules."[31]

The oligonucletides used in the ODM technique, in contrast, have not resulted from a combination of different DNA molecules but are – as already mentioned – with the exception of one or a few nucleotides[32], identical to the corresponding site in the genome of the treated plant cells.

In any case, according to Annex I A, Part 1, No. 1 the new combinations of genetic material in the recipient organism must also be capable of continued propagation in order to fall under the scope of the regulation. This is not the case here either: the oligonucleotide used as the mutagen of the ODM is not capable of propagation because it cannot replicate itself.

2. CRISPR-Cas9

The guideRNA used to apply the CRISPR-Cas9 technique undoubtedly is a recombinant nucleic acid molecule. However, the wording in Annex I A, Part 1, No. 1 implies that the term

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[29] Jackson DA, Symons RH, Berg P. Biochemical Method for Inserting New Genetic Information into DNA of Simian Virus 40: Circular SV40 DNA Molecules Containing Lambda Phage Genes and the Galactose Operon of Escherichia coli. Proceedings of the National Academy of Sciences of the United States of America. 1972;69(10):2904-2909.

[30] Cohen SN, Chang ACY, Boyer HW, Helling RB. Construction of Biologically Functional Bacterial Plasmids In Vitro. Proceedings of the National Academy of Sciences of the United States of America. 1973;70(11):3240-3244.

[31] See EFSA Response to Mandate M-2015-0183 ("Request for EFSA to provide technical assistance with regard to issues related to the legal analysis of new plant breeding techniques") Question 1, http://registerofquestions.efsa.europa.eu/roqFrontend/wicket/page?6-1.ILinkListener-mandateForm-documents-2-fileNameLnk,accessed on 4 November 2015.

[32] Nucleotides are the building blocks that make up DNA molecules. Individual nucleotides do not contain genetic information.

"use of recombinant nucleic acid molecules" does imply some kind of integration into a genome and its propagation which is not possible with RNA.

III. Recital 17

Finally, recital 17 does not preclude application of the exemption rule either. The recital does not restrict the scope of Annex I B to conventional methods (see 1. below). Rather, against the background of the protective purpose of the Directive and the precautionary principle, it verifies the intention of the legislator to exclude methods which have a long safety record from the scope of the Directive (see point 2. below).

1. Regulatory content

According to recital 17, "the 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." At the time of the adoption of the Directive this was understood to include techniques in which the genetic modification took place, *inter alia*, by chemical, radiation or tissue culture methods.[33] However, it cannot be derived from this that the exemption rule of Annex I B is restricted to this technique of mutagenesis, which was deemed conventional in 2001 and has a long safety record.[34]

Firstly, this does not follow from the wording of the exemption criteria. There is no reference there to a restriction to specific techniques of mutagenesis.

Moreover, this would mean that any new or improved methods of mutagenesis developed after the entry into force of the Directive would be excluded from the scope of the exemption rule. Such a far-reaching meaning cannot be derived from recital 17. It would also contradict the wording of the Directive, which in Annex I B, No. 1 completely excludes mutagenesis from its scope.

Recital 17 does not restrict the scope of the exemption rule; rather it merely reaffirms the legislator's intention to specifically exclude from its scope techniques which have been conventionally used in a number of applications and which have a long safety record.

2. The precautionary principle

In this respect, recital 17 reflects the protective purpose of the Directive and the precautionary principle. The protective purpose of the Directive must also be taken into consideration in when interpreting the exemption criteria. According to Article 1(1), the purpose of the Directive is to "protect human health and the environment". Thereby the risk assessment applies only to modifications generated with this technology in plants.[35] In this regard, there is consensus among scientists that targeted point mutations generated in plants through ODM or CRISPR-Cas9 give rise to fewer unintended effects than techniques through which random mutations are generated with the help of chemicals or ionising radiation.[36] Viewed against the background

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[33] See also Krämer, *ob. cit.*, marginal number 48; Spranger, *ob. cit.*, p. 25 f.
[34] Unlike Krämer, *ob. cit.*, marginal number 48 ff.; Spranger, *ob. cit*., p. 25 f.
[35] Spranger, *ob. cit*., takes a different view on this.
[36] See also in this regard:

- New Techniques Working Group, Final Report, point 5.1.5 B ("All experts agree that ODM results in changes in organism that can be obtained with other forms of mutagenesis. They also noted that ODM is expected to generate fewer unintentional changes or effects than those introduced into organisms by irradiation or chemical mutagenesis, which is listed under indent 1 of Annex IB […] "as a technique of genetic modification yielding organisms to be excluded from the Directive");
- EFSA "Scientific opinion addressing the safety assessment of plants developed using Zinc

of the precautionary principle, a general exclusion of new mutagenesis techniques from the scope of Annex I B, No. 1 is not convincing either.[37] If, as is the case here, a new mutagenesis technique is safer than one which indisputably falls within the scope of Annex I B[38], the exemption rule must certainly also apply to that new technique.

IV. Interim result

Organisms which exhibit point mutations induced through the use of ODM and CRISPR-Cas9 techniques would fall within the scope of application of Annex I B, No. 1 if they were regarded as GMO. The classification as a mutagenesis technique is also shared by the EFSA.[39]

The application of Annex I B, No. 1 is not precluded by recital 17 either. This recital does not restrict the exemption to conventional mutagenesis techniques; rather it only reflects the legislator's intention to exclude from the scope of the Directive methods which have conventionally been used and which have a long safety record.

Point mutations induced through the techniques in question here are not distinguishable from changes which have been caused by natural and induced mutagenesis. In this respect, the protective purpose of the Directive expressed in recital 17 does not oppose classification as a technique within the meaning of Annex I B, No. 1.

D. Classification under Annex I A, Part 1

Finally, a general classification of the new plant breeding techniques under the scope of application of Annex I A, Part 1 is prohibited.[40] Instead a differentiated analysis is required, taking into account the specific application of the respective technique. This is illustrated, *inter alia*, by the example of the RTDS technique (a type of ODM) employed by Cibus.

I. Not a technique in the sense of Annex I A, Part 1, No. 1

The RTDS technique employed by Cibus does not fall within the scope of Annex I A, Part 1, No. 1. as it is not in the category of "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":

Firstly, the GRONs (gene repair oligonucleotides) which the Cibus company uses for RTDS techniques are not nucleic acid molecules but synthetic molecules consisting of oligonucleotides and additional chemical groups located at their 5' and 3' ends. Furthermore, the technique does not involve inserting the GRONs into viruses, viroids, bacterial plasmids or other vector systems. Lastly, the GRONs are only temporarily (transiently) inserted into individual plant cells where they unfold their mutagenic effect and are subsequently degraded

Finger Nuclease 3 and other Site-Directed Nucleases with similar function", EFSA Journal 2012;10(10):2943

[37] Unlike Spranger, *ob. cit.*, p. 26 ff., who assumes an "entirely insufficient safety record" for the new technologies, but does not restrict this to the use of point mutations.

[38] See Krämer, *ob. cit.*, marginal number 67: "The fact that a targeted change to heritable material is likely to have less side-effects than a random mutation […]".

[39] See EFSA Response to Mandate M-2015-0183 ("Request for EFSA to provide technical assistance with regard to issues related to the legal analysis of new plant breeding techniques") Question 2, http://registerofquestions.efsa.europa.eu/roqFrontend/wicket/page?6-1.ILinkListener-mandateForm-documents-2-fileNameLnk,accessed on 4 November 2015.

[40] Unlike Spranger, *ob. cit.*, p. 12 ff., 20 ff. and 33, who regards organisms generated by means of the new technologies as falling within the scope of application of Annex I A, Part 1, No. 1 and No. 2.

within a short space of time. The GRONs are neither capable of propagation in the host organism nor do they remain there.

It is important, however, that no new combinations of genetic material are formed during the RTDS process. In the case of the herbicide-tolerant oilseed rape variety developed by the company Cibus, the sequence of the oligonucleotide component contained in the GRONs was, with the exception of one nucleotide, identical to the sequence of the corresponding genome fragment in the treated plant cells. The genetic modification induced through RTDS consists solely of the exchange of one base pair in the oilseed rape genome. Consequently, a recombination of nucleic acid molecules (= a new combination resulting from the joining together of nucleic acid molecules) does not take place in the RTDS process.[41]

II. Not a technique in the sense of Annex I A, Part 1, No. 2

RTDS is also not a "technique involving the direct introduction into an organism of heritable material prepared outside the organism and which do not occur naturally in it". Heritable material denotes the biologically active DNA.[42] However, biological activity of DNA is characterised by its capacity for replication and transcription. The nucleic acid component of the GRONs employed by the company Cibus in the RTDS process is chemically modified at its 5' and 3' ends in such a way that the GRONs cannot be transcribed or replicated. As already described above, the GRONs are only temporarily introduced into individual plant cells and do not remain there. Therefore, the GRONs do not constitute "heritable material".

III. Interim result

Accordingly, the techniques in question here do not fall within the scope of application of Annex I A, Part 1. They do not involve the use of nucleic acid molecules within the meaning of No. 1, nor is heritable material introduced into an organism within the meaning of No. 2.

E. Summary of the results

It can thus be concluded that plants which exhibit point mutations induced by means of ODM and CRISPR-Cas9 techniques do not constitute GMOs within the meaning of the Directive. It is not only the use of a genetic engineering method that is decisive for classification as GMO but also the resulting product. This must differ from plants which could also arise through conventional breeding methods. For the point mutations in question here, this is not the case. Those genetic modifications could also arise through other mutagenesis techniques.

Even if such plants were regarded as GMO, the exemption rule of Article 3(1) in conjunction with Annex I B, No. 1 would apply, as causing point mutations by the application of new plant breeding techniques could be regarded as a mutagenesis technique. The fact that it is a new technique that is being dealt with does not contradict this conclusion either. For recital 17 merely reflects the legislator's intention to exclude methods which have conventionally been used and which have a long safety record from the scope of application of the Directive. Due to the fact that the induced modifications could also be generated through conventional mutagenesis techniques and are not distinguishable from them, the protective purpose of the Directive also does not preclude application of the exemption rule.

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[41] For an interpretation of the terms "recombination of nucleic acid molecules" and "nucleic acid recombination techniques" see the response of the EFSA of 15 October 2015 to the EU Commission's request for a definition of the term "recombinant nucleic acid molecule": "[…] a recombinant nucleic acid molecule can be defined as a molecule that is generated by joining two nucleic acid molecules." http://registerofquestions.efsa.europa.eu/roqFrontend/wicket/page?6-1.ILinkListener-mandateForm-documents-2-fileNameLnk, accessed on 4 November 2015.

[42] *Cf.* Ronellenfitsch, *ob. cit.*, § 3 GenTG, marginal number 91.

Finally, the ODM and CRISPR-Cas9 techniques for inducing point mutations in question here do not fall within the scope of application of Annex I A, Part 1. Thus, for example, the RTDS technique does not lead to the formation of new combinations of genetic material in the sense of No. 1, nor is heritable material introduced into an organism in the sense of No. 2.