

Legal questions concerning new methods for changing the genetic conditions in plants

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Executive summary

There is a lack of consensus among scientists, whether new breeding techniques such as the ODM technique or the CRISPR/Cas technique fall under the field of application of Directive 2001/18/EC.

The lack of scientific consensus on the classification of the new breeding techniques does not allow an interpretation of Directive 2001/18 solely on the basis of scientific criteria. A legal interpretation of the Directive leads to the conclusion that both the ODM technique and the CRISPR/Cas technique constitute GMO techniques which are covered by the field of application of Directive 2001/18.

The classification of a specific technique does not depend on the question, whether the modified organism can be distinguished from an organism that mutated naturally or with the help of traditional breeding techniques (chemicals or radiation); Directive 2001/18 is process-oriented, not result-oriented.

Further, the distinction between what is exempted from the field of application of the Directive depends on what was used as conventional breeding and had a long safety record, when the Directive was adopted.

A legal interpretation of the Directive leads to the conclusion that both the ODM technique and the CRISPR/Cas technique constitute GMO techniques which are covered by the field of application of Directive 2001/18.

The German Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) had classified RTDS oilseed rape, an ODM technique, as not falling under the field of application of the German Gentechnikgesetz. This Decision was based on German law. An examination of the RTDS technique on the basis of Directive 2001/18 would have required to classify the technique as a GMO technique.

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(1) This legal study tries to give an answer to the following questions:

Question I: How to apply the definition of Directive 2001/18 to techniques which are used to change genetic conditions by insertion of material into the cells but without necessarily inserting new DNA into the genome:

- genetic modifications by use of oligonucleotides;
- nuclease such as CRISPR/Cas used to silence genes or induce mutation as a targeted region.

Question II: In the light of these findings: are the decisions made by German authorities on the product of RTDS oilseed rape correct, incorrect, or is there a level of legal uncertainty?

Question III: Is a national regulatory body competent to take decisions on the legal status of relevant products such as RTDS oilseed rape to define them as falling within or without the regulatory scope of the EU Directive?

These questions will be discussed successively.

Section I

Question I: Does Directive 2001/18 cover genetic modifications by use of oligonucleotides and nucleases such as CRISPR/Cas?

I.1 The relevant EU legislation

(2) Directive 2001/18/EC was adopted in 2001.¹ A genetically modified organism (GMO) is defined in Article 2(2) of the Directive 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: (a) genetic modification occurs at least through the use of the techniques listed in Annex I A part 1; (b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification*".

(3) Annex I A Part 1 lists "*inter alia*" techniques which constitute techniques of genetic modification." It reads: "*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 a 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 combination of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally*". Annex I A Part 2 lists techniques "*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 or other than those excluded by Annex I B*".

(4) Recital 17 of the Directive 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*".

(5) Article 3, with the title "*Exemptions*" determines: "*1. This Directive shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B. 2...*"

(6) Finally, Annex I B reads: "*Techniques referred to in Article 3. Techniques/methods of genetic modification yielding organisms to be excluded from this Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than*

¹ Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220, OJ 2001, L 106 p.1.

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".

(7) Annex I B of Directive 2001/18 is almost identical to Annex I B of Directive 90/220² which was repealed by Directive 2001/18, though it is important to underline that the reference to the use of recombinant nucleic acid molecules lacked in Directive 90/220 and was only introduced by Directive 2001/18.³ Also the present Recital 17 of Directive 2001/18 is essentially identical to Recital 7 of Directive 90/220.⁴

(8) It follows from the definition of GMO in Article 2(2) that Directive 2001/18 is a directive which is "process-based": it covers organisms that are generated by a specific process (*"the genetic material has been altered in a way."*). 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.⁵ This means that Directive 2001/18 intends to regulate certain techniques which it considers of being able to constitute a risk to human health or the environment. Recital 17 conforms with this understanding, as it considers that conventional breeding methods which have *"a long safety record"* do not need to be subjected to the regulatory provisions of Directive 2001/18.

2 Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms, OJ 1990, L 117, p.15.

3 Directive 90/220 (fn.2, above), Annex I B: *"Techniques referred to in Article 3. Techniques of genetic modification to be excluded from this Directive, on condition that they do not involve the use of GMOs as recipient or parental organisms, are: (1) mutagenesis (2) cell fusion (including protoplast fusion) of plant cells where the resulting organisms can also be produced by traditional breeding methods"*.

4 Directive 90/220 (fn.2, above), Recital 7: *"Whereas 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"*.

5 This is general opinion. However, the "New Techniques Working Group" which the European Commission set up in 2007, delivered a Final Report in January 2012. This Report was never officially published, but is generally available (www.infogm.org/IMG/doc/ue_working-group-nouvelles-techniques-modifications-vivant_avril2012.doc) and quoted; it will be quoted hereafter as "NTWG Report". It stated (p.6), without giving any reasoning for that opinion, that Directive 2001/18 could be understood as either putting the emphasis on the technique: *"the resulting organism is a GMO, even if the same modification or an intended organism could be obtained by the techniques listed in Annex I A part 2 or Annex I B of Directive 2001/18"*. Or it could be understood to mean that *"the emphasis is on the resulting organism; if the resulting organism is indistinguishable from an organism obtained from natural processes, conventional breeding or by application of the techniques listed in Annex I A Part 2 of annex I B of Directive 2001/18.. then it cannot be considered as a GMO and would therefore be considered out of the scope of the Directive[s]"*. This opinion is not shared here. The text of Directive 2001/18 is unequivocal in this regard. The Directive applies, when an organism is *"altered in a way."* This describes the *way*, not the *end result* of the process of genetic modification.

(9) The substantive objective of Directive 2001/18 is the protection of human health and the environment.⁶ In order to ensure this protection, the Directive bases itself on the precautionary and prevention⁷ principles. In particular, the precautionary principle received considerable importance in the Directive. It is not only mentioned in Recital 8⁸, but also in Article 1, where the objective of the Directive is laid down "*in accordance with the precautionary principle*", and in Article 4(1) of the Directive, where it is stated that "*in accordance with the precautionary principle, Member States [shall] ensure that all appropriate measures are taken to avoid adverse effects on human health and the environment*" (emphasis added). And it is again mentioned in Annex II B to the Directive which deals with the environmental risk assessment.

(10) Every release into the environment of a GMO must be preceded by an environmental risk assessment (Article 4(3) and Annex II). The objective of this environmental risk assessment is "*to identify and evaluate potential adverse effects of the GMO, either direct or indirect, immediate or delayed*".

(11) Releases into the environment must be authorised (Articles 6, 15 and 19); the authorisation must be based on detailed information by the applicant on studies, field tests and other research which he had made. Organisms and products that are released shall bear a label which indicates that they contain GMOs (Article 19 and Annex IV). The responsible person is obliged to carry out a post-marketing monitoring, in order to identify the occurrence of adverse effects of the GMO (Article 19 and Annex VII).

(12) With these and its other rules, the Directive established a detailed system of provisions which have the objective to prevent adverse effects of a GMO for humans or for the environment.

(13) It is in the light of these objectives and detailed provisions that the interpretation of Article 3 and Annex I B of the Directive must be undertaken.

1.2 ODM techniques and their *scientific* classification

(14) There are several terms applied on the usage of oligonucleotides. While the term "Oligonucleotide Directed Mutagenesis" (ODM), which is mostly used in plant breeding, suggests that the technology belongs to the group of

⁶ Directive 2001/18 (fn.1, above), Article 1: "*the objective of this Directive is... to protect human health and the environment*". Recital 4: "*Living organisms... may reproduce in the environment and cross national frontiers thereby affecting other Member States. The effects of such releases on the environment may be irreversible*". Recital 5: "*The protection of human health and the environment requires that due attention be given to controlling risks from the deliberate release into the environment of genetically modified organisms (GMOs)*".

⁷ Directive 2001/18 (fn.1, above), Recital 6: "*Under the Treaty, action by the Community relating to the environment should be based on the principle that preventive action should be taken*".

⁸ Directive 2001/18 (fn.1, above), Recital 8: "*The precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it*".

mutagenesis technologies, other terms such as "oligo-mediated genome editing"⁹, "oligonucleotide-directed gene-editing technology"¹⁰ and "oligo-mediated genome engineering"¹¹ are used in a medical context. This shows that the context may be relevant for defining whether usage of oligonucleotides is regarded a mutagenesis or genome editing/genetic engineering. The difference in the terms is due to the technical details of the technology. In summary, the process used in oligonucleotide technology makes use of genetic material prepared outside the cell and thus has strong parallels to genetic engineering. Some products derived from this process might, though, appear similar to those derived from mutagenesis.

(15) With regard to Directive 2001/18 these differences are relevant. First, the Directive emphasises that the process is decisive for defining what is covered by the Directive and what is exempted. Second, if the process is regarded as a mutagenesis, the use of recombinant DNA might be used as the most relevant criterion; if the use of oligonucleotides is not regarded as mutagenesis, other criteria will also have to be taken into account. Third, mutagenesis is known for many years, while genome editing is a recent technology.

These considerations will be elaborated hereafter:

(16) According to those provisions of Article 3 and Annex I B of Directive 2001/18, organisms which were obtained by mutagenesis, are exempted from the Directive, provided the process which led to the mutagenesis did not involve the use of recombinant nucleic acid molecules.

(17) The terms "mutagenesis" and "recombinant nucleic acid molecules" are not defined in Directive 2001/18. Mutagenesis is the process which leads to the mutation of an organism.

(18) A mutation is a process by which the genetic information of an organism is changed in a stable manner through external influence. Such mutations may occur spontaneously in nature. However, mutations in plants or animals may also be induced by the use of chemicals or of radiation. The use of radiation or chemicals results in a number of smaller or larger deletions or changes in the genome of the receiving organism, which may introduce new properties (random mutation). These properties are then selected in order to make use of the mutation.

9 Disterer, P.- Papaioannou, I.- Evans, C. - Simons, J.P., - Owen, J.S.: Oligonucleotide-mediated gene editing is underestimated in cells expressing mutated green fluorescent protein and is positively associated with target protein expression, *Journal of Gene Medicine* 2012, Vol. 14 No 2, p. 109.

10 Papaioannou, I. - Simons, J.P. - Owen, J.S.: Oligonucleotide-directed gene-editing technology: mechanisms and future prospects. *Expert Opinion on Biological Therapy* 2012, Vol.12 No.3, p.329

11 Di Carlo, J.E. - Conley, A.J. - Penttilä, M. - Wang, H.H.- Curch, G.M.: Yeast oligo-mediated genome engineering. *ACS Synthetic Biology* 2013, p.741.

(19) The technique of influencing mutations of organisms - in particular plants - by means of chemicals or radiation was developed about a hundred years ago and was successfully applied in breeding since then. Authorities did not find significant adverse effects in commercial plant varieties developed by the technique.

(20) Since about fifteen years ago¹², it has become possible to generate changes in DNA composition with the help of so-called oligonucleotides. The technique is called "oligonucleotide-directed mutagenesis" (ODM) or "genome-editing" (see above).¹³ This technique uses DNA components, called oligonucleotides, which are synthetically produced outside the organism. They have a sequence which is identical to the DNA sequence in the target DNA sequence in the cell, except for one or several nucleotides.

(21) The term "oligonucleotide" is not defined in EU law. It is apparently not either precisely defined in science. There is scientific consensus, though, that oligonucleotides are short DNA or RNA molecules which are composed of different nucleotides. The nucleotides can interfere with the gene expression of the cell. Generally, oligonucleotides¹⁴ are considered to be composed of between 2 and 30 nucleotides. However, there appears to be no scientific consensus in this regard: the Dutch Commissie for Genetische Modificatie (COGEM) reports that the term changed over time according to what could be synthesised in laboratories and that, at present, nucleic acids up to 120 may be produced and are still considered oligonucleotides.¹⁵ Thus, the term of oligonucleotides, as a scientific, but not a legal term, depends on the development of science: *"the terms 'recombinant nucleic acids' and 'oligonucleotide' are used more or less intuitively by scientists to indicate certain categories of nucleic acids, but they are not sharply defined. What exactly is indicated by them has changed over time. In the 80s, an 'oligonucleotide' was understood to be a DNA molecule with a length of about 12 to 20 nucleotides. This was what DNA synthesisers could make. Today, that limit has been stretched to approximately 200 nucleotides, and both RNA and DNA*

12 ACRE, the United Kingdom Advisory Committee on Releases to the Environment: New techniques used in plant breeding. Advice of 18 July 2013, https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/239542/new-techniques-used-in-plant-breeding.pdf reports, p.28, that the first studies in this regard were made since 1999.

13 Other names used are targeted nucleotide exchange, chimeraplasty, oligonucleotide-mediated gene editing, chimeric oligonucleotide-dependent mismatch repair, oligonucleotide-mediated gene repair, triplex-forming oligonucleotide-induced recombination, oligonucleotide-directed gene modification, therapeutic nucleic acid repair approach and targeted gene repair, see ACRE (fn.10) p.27; Zentrale Kommission für die Biologische Sicherheit (ZBKS), Stellungnahme der ZBKS zu neuen Techniken für die Pflanzenzüchtung, Az.:402.45310.0104, Juni 2012, p.6; Bundesamt für Umwelt (Schweiz), Neue Pflanzenschutzverfahren, Dezember 2012,p.16.

14 The word "oligo" stems from classical Greek and means "few".

15 COGEM (NL): The status of oligonucleotides within the context of site-directed mutagenesis, CGM/100701-03 of 1 July 2010, p.7.

molecules can be made. For scientific purposes, an exact definition is neither relevant nor useful".¹⁶

(22) In the case of ODM, the oligonucleotide which is introduced into the cell, consists, as mentioned, of nucleotides which are identical with that of the target cell - except one or few nucleotides¹⁷. The target cell then appears to activate its repair mechanism and absorb the new inserted nucleotide. The oligonucleotide itself is probably dissolved within the cell.

(23) There is consensus among scientists that it is not altogether clear until now, how the process of targeted mutation occurs in detail. *"The process by which these oligonucleotides can cause modifications remains largely unclear".¹⁸*

(24) There is no scientific consensus either, whether an oligonucleotide is a recombinant nucleic acid. As mentioned above, EU law does not contain a definition of this term. Sometimes it is argued that, as a synthetic oligonucleotide only links different nucleotides, but does not use existing pieces of DNA or RNA, there is no combination of DNA or RNA, and therefore oligonucleotides are not recombinant nucleic acids. Other scientists argue that an oligonucleotide is combined out of single nucleotides, some identical to the genome of the target cell, others ("one or few") not. This constitutes, according to these scientists, a combination so that, by definition, an oligonucleotide is a recombinant nucleic acid, independent of the number of nucleotides.

(25) This lack of scientific consensus is demonstrated by the following statements:

(26) *"The question, whether an oligonucleotide is a recombinant nucleic acid, does not have a simple answer. Depending on the context, an oligonucleotide may or may not be regarded as a recombinant nucleic acid. As an arbitrary limit at which an oligonucleotide should not be considered a recombinant nucleic acid, a difference of one in twenty oligonucleotides could be used"¹⁹.*

16 COGEM (fn 15, above), p.14

17 See also Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) Decision of 5 February 2015: *"ggf. mit einer Abweichung von einem oder wenigen Nukleotiden"* (eventually with a deviation of one or few nucleotides; my translation) .

18 COGEM (fn15, above), p.8; see also ZKBS (fn 13, above), p.6. *"Die zellulären Mechanismen, die jeweils zur Mutation führen, sind nicht völlig verstanden"* (the cellular mechanisms which lead to the mutation in each individual case, are not fully understood). see also Bundesamt für Umwelt (Schweiz) (fn 13, above), p.16: *"Die Mutationen erfolgen, so wird vermutet, durch den zelleigenen Genreparaturmechanismus.. Was das Schicksal der Oligos betrifft, so wird erwartet, dass die zugefügten Oligos nicht ins Erbgut integrieren, sondern innerhalb der Zelle abgebaut werden"* ("the mutations occur, it is presumed, by the cell's gene repair mechanism.. As regards the destiny of the oligonucleotides, it is expected that the added oligonucleotides do not integrate into the genome, but are dissolved within the cell"; my translation).

19 COGEM (fn.15, above), p.15.

(27) *"There was a discussion on how many nucleotides could constitute a new combination of genetic material/nucleic acid in this context. A majority of experts concluded that in order to form a new combination, a nucleotide sequence of at least 20 basic pairs is required. A minority of experts were of the opinion that under the current definition, the replacement of only one nucleotide in a nucleic acid molecule could be interpreted as producing a recombinant nucleic acid... A majority of experts were of the view that oligonucleotides in this technique cannot be considered as recombinant nucleic acids in the sense of Annex I Part B of Directive 2001/17/EC. For a minority of experts it is not possible to arrive at this conclusion"*²⁰.

(28) *"A legal as well as a scientific definition [of oligonucleotides] lack. Thus, it depends on interpretation whether oligonucleotides are recombinant nucleic acids or not"*.²¹

(29) *"Even changing a single gene, whether it encodes an enzyme, a structural protein, a peptide hormone or a regulatory protein, can cause unintended functional or structural disturbances at the level of the cell and the organism as a whole"*²².

(30) *"The oligonucleotides which are introduced into the cells, are not new combinations of genetic material, as their sequence follows that of the target sequence..., eventually with a deviation of one or few nucleotides"*²³.

(31) *"If ODM is defined as a GM technique, then the organisms produced should be excluded from the legislation. ACRE advises that oligonucleotides that are used in site-directed mutagenesis should not be considered as being recombinant nucleic acids and thus ODM is captured by Annex IB... Where these molecules [molecules that are used in techniques such as ODM and zinc finger nuclease (ZfN)-induced mutations] are transiently present in host cells and do not integrate into the host's genome, ACRE considers that their classification as recombinant nucleic acids is not relevant from a scientific point of view"*²⁴.

(32) It must thus be concluded that the scientific classification of OGM technique does not help, as there are diverging opinions and it is not possible to declare the opinion of a majority of scientists or group of scientists to be decisive. This is all the more so, as several of the experts or experts groups are rather cautious in their formulation, arguing that the ODM technique "should" be classified in a specific sense, but not that it "must" be classified in this sense. This means that other considerations may also have influenced the scientific opinion, such as the

20 NTWG Report (fn.5, above), p.6.

21 Bundesamt für Umwelt (fn.13, above), p.23.

22 John Fagan - Michael Antoniou - Claire Robinson: GMO myths and truths. Earth Open Source, (London 2012); earthopensource.org/earth-open-source-reports/gmo-myth-and-truth-2nd-edition

23 ZBSK (fn.13, above), p.6.

24 ACRE (fn 12, above), p.29. (Emphasis added).

fact that "*organisms developed through ODM could in many cases not be distinguished at the molecular level from those developed through 'traditional' mutation techniques (using chemicals or ionizing radiation) or from wild-type organisms*"²⁵. However, this might change in the future and it is not possible to make the legal interpretation of a term entirely dependent on the state of scientific knowledge.

(33) Furthermore, COGEM rightly pointed out²⁶ that when synthetic oligonucleotides are not classified as recombinant nucleic acids, this might lead to new problems, such as the creation of synthetic micro-organisms which would not be covered by Directive 2001/18.

(34) For a scientist, it may make sense to differentiate between such targeted mutations which can be detected and those which are not capable of being detected, as this influences the scientists' work. However, this is a reasoning which argues from a scientific perspective and leaves aside the reasoning on the legislation as it stands.

(35) It cannot be excluded that the scientific experts opinions, how to classify the OGM method, is influenced by their concern, how this technique should be classified in future rather than by their assessment, how it is to be classified at present under the definition of Directive 2001/18.

(36) It is obvious from the above quotations that there is no consensus among scientists, whether an oligonucleotide is a recombinant nucleic acid or not. Some admit that the number of 20 nucleotides in which a synthetically produced oligonucleotide must be different from the DNA of a target cell, is arbitrary²⁷, scientifically not relevant²⁸ and that it has changed over time²⁹. This means that scientific interpretations alone are not able to determine the precise meaning of the exclusion of some forms of mutagenesis foreseen in Annex I B to Directive 2001/18.

I.3 Legal interpretation of Article 3 and Annex I B

(37) The question then arises, whether a legal interpretation of Directive 2001/18 can further clarify the question. In the absence of a scientific and legal definition of both the terms "ODM" and "mutagenesis", and the difference in the understanding of scientific experts, mentioned above, an interpretation based solely on the wording of Annex IB will not lead to results. Rather, it will have to be looked at other means of interpretation, in particular the objective and purpose of Annex IB, the history of Directive 2001/18 and the general system which was introduced by it.

25 ACRE (fn.12, above), p. 30.

26 COGEM (fn.15, above), p.12s.

27 The term "arbitrary" is used twice by COGEM (fn.15, above), p.15.

28 ACRE (fn.12, above), p.29.

29 COGEM (fn.15, above), p.7 and p.14.

(38) The application of Directive 90/220, the predecessor of Directive 2001/18, led to difficulties in the mid-nineties, as the majority of the then EU Member States suspected the European institutions of trying to introduce GM plants into the environment and food chain by force, without potential risks for humans, animals or for the environment being adequately taken into consideration. That position was supported by strong public opposition within the EU to the GMO technique in general. After a voting "incident" at EU level, Member States, with the tacit consent of the European Commission³⁰, practised a de facto "moratorium" for GMO-authorisations, by not granting authorisations for the release into the environment of GMOs under Directive 2001/18.

(39) Then, the United States, Canada and Argentina brought the EU before the Dispute Panel of the World Trade Organisation (WTO), arguing that the moratorium constituted an illegal restriction of international trade. As a consequence of that procedure, the Commission started to introduce new legislation, submitting a proposal for amending Directive 90/220 in February 1998³¹. The European Parliament and the Council, the EU co-legislators, considered this proposal as not sufficient to ensure the protection of humans and the environment and to accommodate the concern of the European public opinion. They therefore decided on the adoption of a completely new directive.

(40) With regard to Directive 90/220, this new Directive, 2001/18, contained a number of elements and provisions which strengthened the objective of protecting humans and the environment. These new elements were in particular the following:

- a reference to the principle of preventive action;
- a repeated reference to the precautionary principle;
- the requirement to make an environmental risk assessment for each release of a GMO and the fixing of a common methodology for it;
- the specific emphasis of also taking into account the long-term cumulative effects of a release³²;

30 There was no explicit decision on the moratorium. Under the present Article 258 of the Treaty on the Functioning of the European Union (at that time Article 226 EC), the Commission could have taken legal action against Member States which did not authorise the release of GMOs, but did not do so.

31 OJ 1998, C 139 p.1.

32 Directive 2001/18 (fn 1, above), Annex II, introduction: "*A general principle for environmental risk assessment is also that an analysis of the 'cumulative long-term effects' relevant to the release and the placing on the market is to be carried out. 'Cumulative long-term effects' refers to the accumulated effects of consents on human health and the environment, including inter alia flora and fauna, soil fertility, soil degradation of organic material, the feed/food chain, biological diversity, animal health and resistance problems in relation to antibiotics*".

- the necessity to respect ethical principles recognised in a Member State and the establishment of a Committee on Ethics³³;
- the consultation of the public³⁴;
- the requirement to monitor the GMOs after they had been released into the environment³⁵;
- the granting of an authorisation only for a fixed period³⁶.

(41) All these provisions had the objective to ensure - in complement to the provisions which had already been laid down in Directive 90/220 and which were repeated in the new Directive 2001/18 - that as far as possible all risks of GMOs for humans or the environment were identified in time, preferably before any release, and covered by appropriate risk management measures. There is not one single provision in Directive 2001/18, where the safety measures with regard to GMOs were reduced in comparison to Directive 90/220. In view of the opposition of the public in the European Union to GMOs in general, this approach is logical and comprehensible. It was the attempt of the legislator to overcome or at least appease the public concern, while at the same time accommodating with the requirements of international trade law.

(42) This political and legal situation is decisive for the interpretation of Annex IB to Directive 2001/18. As far as is of interest for this study, the provision excludes organism produced by mutagenesis, "*on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms*". This formula is different to that of Directive 90/220 which had, in Annex I B, excluded organisms produced by mutagenesis, "*on condition that they do not involve the use of GMOs as recipient or parental organisms*". The reference to "recombinant nucleic acids" was added.

(43) The formula used by Directive 2001/18 puts a supplementary requirement to the mutagenesis process by exempting mutations only when recombinant nucleic acid molecules were not used. This indicates that the legislation, through the adoption of Directive 2001/18, intended to enlarge the field of application of Directive 2001/18 and to reduce the exemption of Article 3 and Annex I B.

(44) It is in the light of the history of Directive 2001/18 and its Annex IB in particular, that Recital 17 of the Directive has to be understood³⁷. This Recital

33 Directive 2001/18 (fn 1, above) , Recital 57 and Article 29.

34 Directive 2001/18 (fn 1, above), Recital 46 and Article 24.

35 Directive 2001/18 (fn 1, above), Recital 43 and Article 20.

36 Directive 2001/18 (fn 1, above), Recital 48 and Article 19.

37 It should be pointed out that practically no scientific publication which addressed the questions of the present study, discussed or even mentioned the existence of Recital 17 and its impact on the interpretation of Annex I B. The one exception is COGEM (fn 15, above) which shortly mentions, p.14, the Recital. ACRE (fn 10, above), admits p.1 that its opinion is based on scientific considerations and that "*Ministers will need to seek a legal*

provides that the Directive shall not apply to techniques “ *which have conventionally been used in a number of applications and have a long safety record*”. Recital 17 does not refer to scientific language, but refers to practical applications and to the experience with the safety of these techniques for humans and the environment.

(45) In 2001, when Directive 2001/18 was adopted, mutation techniques which were in use were techniques inducing a mutation by chemical treatment or by ionising radiation.³⁸ Both techniques had been first applied in the 1920s and since then developed in numerous applications with plants and animals. Authorities did not signal significant negative safety effects on humans or for the environment throughout the period of application of these techniques.

(46) In contrast to this, the ODM technique was of recent date. The very first scientific publications were made in 1999.³⁹ Patents were applied for and attributed much later, around 2010. Thus, it is clear that the ODM technique was, at a time when Directive 2001/18 was adopted in 2001, not a technique that had been applied in a “ *number of applications*”. Therefore, it did not either have a “ *long safety record*” at that time.

(47) With the adoption of Directive 2001/18, the European Parliament and the Council tried to improve the safety net for the release of GMOs and to reduce the risk which such a release could have for human health and the environment. The enlargement of the exemption in Annex IB of “[mutagenesis] *not involving the use of GMOs*” in Directive 90/220 by the addition of the words “[mutagenesis] *not involving the use of recombinant nucleic acid molecules*” in Directive 2001/18 meant to *reduce* the number of exemptions falling under Annex I B. It was not meant to provide for an exemption of new techniques which were largely unknown and where the risks were uncertain.

(48) Recital 17 thus has the function to clarify that only those techniques “ *which have conventionally been used in a number of applications and have a long safety record*” were to be exempted. This provision clearly concerned the techniques of using chemicals or ionising radiation. Indeed, these two techniques had been in use for more than fifty years, when Directive 2001/18 - and its predecessor, Directive 90/220 - were adopted. For these two techniques, legislators estimated that there was a “ *long safety record*” so that the risk of unknown adverse effects from their use would be minimal.

(49) The use of the word “conventionally” supports this interpretation: Recital 17 would also be coherent, if that term had been omitted. Its insertion into the text shows that the Directive intended to exempt such techniques that were well

opinion on our conclusions”

38 The same applies to the techniques mentioned in Annex IA Part2 of Directive 2001/18 which will not be discussed further.

39 Lusser, Maria - Parisi, Claudia - Plan, Damien - Rodriguez Cerezo, Emilio: New plant breeding techniques. State-of-the-art and prospects for commercial developments. Joint Research Centre Technical Report EUR 24760. Rome 2011, p.29; similarly ACRE (fn 12, above), p.28.

known and applied, so that an environmental risk assessment, an authorisation, a post marketing monitoring strategy etc were not necessary to protect human health or the environment. Only this interpretation makes sense, as otherwise Recital 17 and in particular the reference to "*conventional*" techniques and the "*long safety record*" would be incomprehensible.

(50) The message sent to the European public was thus clear and consistent: the new Directive, based on the precautionary principle would ensure that *all* risks from the release of genetically modified organisms would be taken care of and no authorisation would be granted, where there was a doubt, whether such a risk existed. Only those techniques and processes would be exempted from the field of application of the Directive, which had already been in usage and - in relation to the process - had not shown specific risks during their time of usage for humans or the environment.

(51) Recitals are an integral part of EU legislative acts; they may be used for the interpretation of the different provisions of a directive.⁴⁰ In view of the objective of Directive 2001/18 to reduce the risk from releases into the environment and to accommodate the European public opinion which was, in time of discussion and adoption of Directive 2001/18, opposed to the GMO technique, the term "*recombinant nucleic acid molecules*" of Annex I B must be legally understood to also include oligonucleotides where only one or few nucleotides were modified. Consequently, a change in the genetic material which is generated through the use of the ODM technique, must be considered to be a process which involves the use of recombinant nucleic acid molecules as well as a process that involves material prepared outside the organism and then injected to the cells. This technique is therefore not exempted from the application of Directive 2001/18.

(52) As explained, the process of introducing oligonucleotides into cells does not have any similarity with random mutagenesis. Rather, this process has to be considered as a genome editing. The use of oligonucleotides generally cannot be regarded as mutagenesis in the sense of Directive 2001/18. therefore, also other criteria, such as indicated in the Directive, Annex I A, Part 1, have to be taken into account

(53) This result is not put into question by the fact that a change to genetic material induced by the ODM technique cannot, in some cases, be distinguished from a naturally occurring mutations. First, the detectability of the technique which was used, is a requirement for the authorisation of the release⁴¹; this means that a GMO which cannot be detected, is nevertheless a GMO. It is then up to the company which wants to release the GMO into the environment, to ensure that the GMO can be detected. And nowhere in Directive 2001/18 is there any provision which provides that a GMO-plant which cannot be distinguished from a non-GMO plant, is not coming into the field of application of the Directive. Second, the present state of scientific knowledge concerning the possibility to distinguish between a naturally occurring mutation and a change induced by

40 Court of Justice, cases C-355/95P, TWD, E.C.R 1997, p.I-2549; T-270/97, EPAC, E.C.R 2000, p.II-2267.

41 Directive 2001/18 (fn.1, above), Article 13(2) and Annex III A, II C(2)(f) and (g), IV B (5), V A (1)

ODM techniques might alter at any moment in future and enable the making of such a distinction. Third, it must not be overlooked that the use of the ODM technique may be subsequently used several times with the same organism. This could lead to quite substantial changes in the genome of plants or animals. Allowing such changes to happen without the safeguards which were introduced by Directive 2001/18 would mean that GMOs would be allowed to be released into the environment; this would put into question the very purpose of Directive 2001/18. As the EU legislator decided to adopt a process-related directive and not to look at the final result of the genetic modification, the possibility to distinguish between such GMO-processes and naturally occurring mutations cannot be decisive.⁴²

I.4 Nucleases such as CRISPR/Cas

(54) Nucleases are enzymes which may be synthetically produced outside a cell. They may be so constructed that they cut the DNA of a cell at a specific place. Then, the natural repair mechanism of the cell is triggered to repair the DNA. During this process mutations, deletions or inserts of new sequences or genes can be induced.

(55) The classification of CRISPR/Cas as genome editing is very common in the medical sector as well as is the case with the use of other nucleases such as zinc finger and TALENs⁴³. Again, the process used makes usage of material prepared outside the cell and thus has a strong parallel to genetic engineering, even if some products derived from this process might appear similar to those that can be derived from mutagenesis.

(56) As nuclease techniques embrace several different techniques, which might be different from one to the other, the following discussion will limit itself to the CRISPR/Cas technique. This technique is described as follows⁴⁴:

(57) *"The CRISPR-Cas system consists of two RNA molecules and a protein. The first RNA molecule can bind to a specific DNA sequence of 20 nucleotides, the second RNA molecule binds to the first, and then the Cas protein can bind. When a protospacer adjacent motif (PAM) is present next to the sequence to which the first RNA molecule binds, the Cas9 protein cuts each strand of the double helix DNA molecule, thus causing a double strand break in the DNA. .. The application of CRISPR-Cas as a gene or genome editing system is based on the possibility of*

42 Scientists argue in favour of a change in the orientation of the EU GMO-legislation: this legislation should not look at the process of making a product (by means of GMO techniques), but at the final result of the process (whether the final product has new characteristics); see GENOM (NL) Should EU legislation be updated? Scientific developments throw new light on the process and product approaches, COGEM Report CGM/090626-03 [without year]; COGEM (fn 15, above); ACRE (fn 12, above). A discussion of this political issue goes beyond the present legal study.

43 See http://en.wikipedia.org/wiki/Genome_editing.

44 COGEM: CRISPR-Cas - Revolution from the lab. COGEM Report and advice [without year] CGM/141030-01, section 2.1.

introducing breaks into genome sequences at specific places and on the use of cellular DNA repair mechanisms to introduce mutations and deletions or insert new sequences".

(58) RNA is a recombinant nucleic acid molecule which is prepared outside the organism and then introduced into the cell, alone or in combination with the Cas9 protein. The technique leads to changes in the sequence of the genome that do not occur naturally. Applications of the system vary: for some applications, parts of the CRISPR/Cas system are inserted into the genome; for other applications, a vector system - such as a genetically modified virus - is used to introduce the system into the targeted cell. The detailed processes which occur are again not completely known. Scientists observed a number of side effects when this technique was used.⁴⁵

(59) One decisive point for a legal assessment is that heritable material produced outside the target organism is introduced into that organism. This makes the technique one which falls under the provisions of Article 2(2) and Annex I A part I of Directive 2001/18, all the more as the enumeration of techniques which are used to qualify a technique as a technique coming under that provision is not exhaustive.

(60) Technically, the process of applying CRISPR/Cas in cells does not have any similarity with random mutagenesis. This process is nothing else but what is called genome editing. Therefore, the use of CRISPR/Cas generally cannot be regarded as mutagenesis in the sense of the Directive. It follows from this that also other criteria such as defined in the Directive, Annex I A, Part 1, have to be taken into account.⁴⁶

(61) As discussed above, the fact that the result obtained is similar to a result which may occur spontaneously in nature, is again not relevant, as Directive 2001/18 deals with the *process* of modification, not with the end *result*. For the same reason, the circumstance that organisms with a targeted change caused by the CRISPR/Cas system cannot be distinguished from organisms which had not been genetically modified is not relevant. Indeed, it was already pointed out above that the question of detectability might change in future, due to new scientific findings.

(62) In view of the difficulty of distinguishing between modified and non-modified organisms, scientists in particular plead for another interpretation of Directive 2001/18, which would exempt the CRISPR/Cas technique from its application.⁴⁷ However, this is a political requirement which has nothing to do with the legal

45 Agapito-Tenfen, S. - Wikmark, O.: Current status of emerging technologies for plant breeding: Biosafety and knowledge gaps of site directed nucleases and oligonucleotide-directed mutagenesis. GenOek-Tromsøe 2015; <http://genok.com/arkiv/4288/>.

46 This refers to "techniques involving the direct introduction into an organism of heritable material prepared outside the organism..." and, furthermore, 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". Both these methods are mentioned in Annex I A.

interpretation of the Directive, and goes beyond the objective of the present study.

I.5 Article 2(2) and Annex I A Part 1 of Directive 2001/18

(63) The application of Article 3 and Annex I B to Directive 2001/18 can thus be excluded. However, it remains to be seen, whether positively, Article 2(2) of the Directive⁴⁸ and Annex I A Part 1⁴⁹ apply, as these provisions lay down which alterations of genetic material are to be considered as coming under the provisions of the Directive.

(64) It was already mentioned that Directive 2001/18 deals with the way in which the genetic material is altered and not, whether the final result of the modification is distinguishable from naturally occurring alterations.

(65) A first statement to make is that certainly changes to genetic material which are induced by repeated, subsequent uses of oligonucleotides for targeted mutations are so exceptional in nature that it cannot seriously be held that they are "naturally occurring". However, such repeated targeted changes may lead to an organism which is significantly modified with regard to the original, not modified organism. The same argument applies when the oligonucleotides are used to modify the genome of an organism at several places. Such modifications do not naturally occur spontaneously.

(66) Furthermore, the wording of Article 2(2) ("*at least*") as well as the wording of Annex I A Part 1 ("*inter alia*") explicitly indicate that the enumeration of techniques in these two provisions is not exhaustive. Other techniques of genetic modification may come under their provisions which are not explicitly enumerated. The precautionary principle, which figures so prominently in different provisions of the Directive, has just the purpose to ensure that in cases of scientific uncertainty - in the present case, the question whether a certain technique is covered by the Directive or not - the stricter, preventive measures of the Directive shall apply. For this reason, the fact that, in Annex I A Part 1 no.1, a vector system is mentioned which transports the recombinant nucleic acid molecules into the host organism, while the ODM technique may not use a vector system, is of no relevance. Determining is rather that the oligonucleotides must be understood, in view of the objective and purpose of Directive 2001 as being recombinant nucleic acid molecules⁵⁰ which are produced outside the target organism and are then incorporated into that organism.

47 Rather typical for this approach are the conclusions by GENOM, Crispr- Cas - Revolution from the lab. COGEM Report and advice CGM/141030-01 [without year], section 7: "*Within the current legal framework, applications of CRISPR-Cas fall under the legislation of GMOs. However, CRISPR-Cas can be used for various purposes, several of which should qualify for exemption from the regulation. New techniques such as CRISPR-Cas show that the current EU GMO legislation is due for revision*". (Emphasis added).

48 See the wording of Article 2(2) of Directive 2001/18, at paragraph 2, above.

49 See the wording of Annex I A Part 1 in paragraph 3, above.

50 See on this paragraph 51, above.

(67) This parallel treatment of the two techniques - with or without a vector system - is also justified by the fact that the processes which occur within the target cell by using the ODM technique are, until now, not fully understood. Risks which might occur by using the technique, are therefore not fully researched. This applies in particular to long-term and cumulative effects. There might be side-effects caused by the inserted material, on proteins or metabolites, finally on the agronomic performance and the quality and safety of the modified organisms⁵¹. The environmental risk assessment of Annex II to Directive 2001/18 was precisely introduced, in order to ensure that unknown risks be examined, before a release could be authorised; this consideration which is based on the precautionary principle, also applies to the new ODM or CRISPR/Cas technique. The fact that a targeted change to heritable material is likely to have less negative side-effects than a random mutation is, in itself, not an argument against the necessity of a detailed examination of the effects of the technique on human health or the environment.

I.6 Answer to Question 1

(68) The answer to Question 1 is that both the genetic modification of organisms through the use of oligonucleotides and through the CRISPR/Cas system are covered by Directive 2001/18/EC.

Section II

Question II: In the light of these findings: Are the decisions by German authorities on the product of RTDS oilseed rape correct, incorrect or is there a level of legal uncertainty?

II.1 The Decisions by the German authorities

(69) The Cibus company had applied to the German Bundesamt für Verbraucherschutz und Lebensmittelsicherheit (BVL) (Federal Office for Consumer Protection and Food Safety) for a decision according to which the oilseed rape lines which had been developed with the help of the Rapid Trait Development System (RTDS), which uses ODM, did not constitute genetically modified organisms according to the German Gentechnikgesetz (GentTG) (Act on Genetical Techniques).

(70) By Decision of 5 February 2015, the BVL adopted a Decision by which it stated that the herbicide resistant oilseed rape lines of the Cibus company did not constitute genetically modified organisms under the German GentTG. It further indicated that this Decision would become invalid, if the European Commission reached a different conclusion under Directive 2001/18. It justified its Decision with the following arguments:

⁵¹ Eckerstorfer, M.- Miklau, M.- Gaugitsch, H.: New plant breeding techniques and risks associated with their application. Umweltbundesamt Austria Report Rep-0477. Vienna 214; Agapito-Tenfen, S.- Wikmark, O. (fn 45, above).

(71) 1. The technique in question did not use integrated vector systems and no new combinations of genetic material were integrated into the genome of the plant.

2. The chemically synthesised and modified oligonucleotides "Gene Repair Oligonucleotides" (GRON) which were introduced transiently did not constitute recombinant nucleic acid molecules or hereditary material in the sense of Article 3 (3) (a) letter (a)(b) GenTG. Their sequence was identical with that of the target sequence, eventually with a deviation of one or several nucleotides.

3. The effect of the GRON-molecules was comparable to that of a chemical molecule, as punctual mutations of one or two nucleotides are introduced at a specific place in the plant genome. These mutations cannot be distinguished from mutations which are caused by natural or chemical mutagenesis. According to Article 3 no.3b, phrase 2 letter a GenTG (mutagenesis) are deemed not to be genetically modified mutations.

(72) BVL concluded that the German GenTG was not applicable.

(73) Several applicants objected to that decision. Their request to quash the Decision was rejected by Decision of the BVL of 1 June 2015. The BVL held the request to be inadmissible, as the applicants were not affected in their own rights. Furthermore, it considered the Decision of 5 February 2015 to be legally correct. It repeated the arguments of the first Decision and further argued that the use of the GRON-molecules which were not integrated into the genome, had the same effects as a chemical mutation, as they were introduced from outside into the cell nucleus, causing targeted changes and were then degraded through the cell-owned system. The targeted mutations caused by GRON were not distinguishable from mutations caused by chemicals or by irradiation or which spontaneously occur in nature. Thus, the process came under the notion of mutagenesis which is, according to Article 3 no 3b GenTG, not a process which is covered by the GenTG.

(74) BVL argued further that also the precautionary principle had been respected. The changes caused by the process in question could not be distinguished from mutations which are caused by chemicals or radiation or which may occur naturally. Mutations caused by chemical and radiation techniques are used in conventional breeding since decades and are not subject to specific authorisation requirements. Also, the RTDS technique presents fewer risks than chemical or radiation techniques, as it is targeted, whereas the treatment with radiation or chemicals caused random mutations.

II.2 Assessment of the Decisions

(75) Question 2 does not require an answer, whether the Decisions of the BVL are in compliance with the German GenTG. The question is rather, whether they comply with Directive 2001/18/EC.

(76) The RTDS system uses, as it can also be concluded from the BVL statement, oligonucleotides, heritable material that was altered and prepared outside the

organisms. These oligonucleotides differ, as the BVL further stated, from the target sequence with regard to one or few nucleotides.

(77) It was stated above that the term "oligonucleotides" lacks a generally recognised legal or scientific definition. Scientists disagree on the question, whether an oligonucleotide, where one or few nucleotides are different from the molecules in the target organisms, already constitutes a recombinant nucleic acid molecule or not. The study therefore discussed, whether the change within the genetic material of the plant was caused by recombinant nucleic acid molecules - then the process would be covered by Directive 2001/18, as the exemption of Article 3 and Annex I B would not apply; or whether oligonucleotides with a deviation of one or few nucleotides did not yet constitute recombinant nucleic acid molecules, as for them at least 20 differences were necessary - then the ODM process, to which RTDS belongs, would be exempted from the application of Directive 2001/18.

(78) The study concluded that the scientific reasoning concerning the ODM process could not be used to give a legal interpretation of Directive 2001/18 and its field of application.

(79) As regards the legal reasoning, it was underlined that Directive 2001/18 considerably strengthened, with regards to its predecessor, Directive 90/220, the preventive and precautionary measures, in order to ensure that only such GMOs were allowed to be released into the environment, which were authorised, which had undergone a detailed environmental risk assessment and which were found not to present a significant risk to humans or to the environment. According to Recital 17, the Directive intended to allow for exemptions from these strict preventive requirements only for those techniques, which had "*conventionally been used in a number of applications*" and which had a "*a long safety record*". The study argued that this objective of the Directive had to be taken into consideration in the legal interpretation of the provision that mutagenesis was exempted when it did not use recombinant nucleic acid molecules. ODM techniques are not equivalent to mutagenesis and had not been used conventionally in a number of applications, when Directive 2001/18 was adopted. This technique did not either have a long safety record. The study concluded that in view of the objective of Directive 2001/18, to ensure as good a protection of humans and the environment as possible, the OGM technique was therefore not covered by the exemption of Article 3 and Annex I B to Directive 2001/18 and came thus under the field of application of that Directive.

(80) If this legal reasoning is correct, then the Decisions by the BVL are not in compliance with the requirements of Directive 2001/18.

II.3 Possible explanations for the Decisions

(81) It should be pointed out that the German GenTG does not contain a provision which transposes Recital 17 of Directive 2001/18 into German law. This might have led BVL to the conclusion that the purpose of the GMO-legislation is

irrelevant and that the only question which it had to answer was, whether the RTDS system provoked a mutagenesis.

(82) The two BVL Decisions referred to an opinion of the German Zentrale Kommission für die Biologische Sicherheit (Central Commission for Biological Safety) ZKBS of 6 February 2015⁵². This Opinion referred back to an earlier Opinion which the ZKBS had issued in June 2012 on new techniques for plant breeding which discussed ODM and other techniques⁵³, and quoted it extensively.

(83) In the opinion of June 2012, ZKBS had argued: "*The ZKBS follows the opinion of NTWG that a sequence must have at least 20 nucleotides, in order to lead to a recombinant nucleic acid. An intentional modification of less than 20 nucleotides cannot be distinguished with sufficient certainty from the accidental occurrence of this sequence. It is correct that certain sequences of less than 20 nucleotides can be detected, but they are not apt to determine their provenance. They cannot be distinguished from genetic modifications caused by conventional mutagenesis or natural mutations. The mutations induced by mutagenesis processes are, according to Article 3 no 3b phrase 2, letter a GenTG (mutagenesis), considered not to be genetically modified modifications*".⁵⁴

The Opinion of 6 February 2015 quoted this earlier Opinion and took as the decisive point the fact that a change of less than 20 nucleotide pairs does not allow to distinguish this process from a spontaneous occurrence of such a sequence with sufficient security. As the RTDS technique led to the introduction into the cell of mutations which did not exceed one or two nucleotide pairs, the technique was not a technique which came under the field of application of the German GenTG.

(84) However, the opinions of ZKBS are erroneous, for two reasons. Firstly, as was mentioned above, a technique producing a GMO must be distinguishable from other techniques. It is therefore not logically possible to conclude from the question, whether a deliberate change can be distinct from a spontaneous mutation to answer whether that technique produces a GMO or not. Secondly, ZKBS wrongly claimed that its opinion was that of the NTWG: NTWG was not of the opinion that a sequence must have at least 20 nucleotide pairs in order to

52 ZKBS, Stellungnahme der ZKBS zu mittels RTDS (Rapid Trait Development system) hergestellten herbizidresistenten Rapslinien der Firma Cibus, of 6 February 2015, Reference no: 42050.

53 ZKBS, Stellungnahme der ZKBS zu neuen Techniken für die Pflanzenzüchtung, June 2012.

54 ZKBS (fn.53, above) section III (my translation): "... dass ein Segment mindestens 20 Nukleotidpaare (NP) umfassen muss, um zu einer rekombinierten Nukleinsäure zu führen.. Eine absichtliche Änderung von weniger als 20 NP kann von dem zufälligen Vorkommen dieser Sequenz nicht hinreichend sicher unterschieden werden. Bestimmte Sequenzen von weniger als 20 NP können zwar nachgewiesen werden, eignen sich jedoch nicht zur Bestimmung ihrer Herkunft. Sie sind nicht von den durch konventionelle Mutagenese oder natürliche Mutation entstandenen genetischen Veränderungen (zufälliges Vorkommen) zu unterscheiden.. Die durch Mutagenese induzierten Mutationen gelten gemäss § 3 Nr.3b Satz 2 Buchst.a GenTG (Mutagenese) nicht als gentechnische Veränderungen".

lead to a recombinant nucleic acid. Rather, on three occasions, the NTWG indicated that there was disagreement among the experts on this question.⁵⁵ The ZBKS opinion wrongly considered the majority opinion in NTWG as the correct opinion and ignored the minority opinion. And the BVL Decisions simply referred to the ZBKS opinion, without further discussing the opinion of the minority group of experts. Such a discussion would have all the more been necessary, as the Decision of 5 February 2015, explicitly stated that the sequence of the oligonucleotides would be identical with the targeted sequence "*eventually with a deviation of one or few nucleotides*". In science, there is no "*de minimis*" provision which allows to set aside smaller deviations. The BVL gives no explanation whatsoever, why the deviation of one or few nucleotides is irrelevant for the final decision and therefore could be ignored.

(85) The comparability of a targeted change with a mutation caused by a chemical mutagen (point 3 of the arguments of the Decision of 5 February 2015 and p.7 of the Decision of 3 June 2015) does not lead anywhere, as one cannot conclude from the comparability of random mutations and targeted changes on the interpretation of Directive 2001/18. In the same way, it could be argued that a targeted change is comparable to what is considered genetic engineering a classical genetic modification, because in both cases modifications of the organism are induced which do not occur naturally.

(86) Both Decisions do not discuss with one word the purpose of Directive 2001/18, as it appears in Recital 17, to only exclude traditional mutation methods which have history of safe use. They assume that "mutagenesis" by traditional breeding techniques is exempted from the field of application of Directive

55 NTWG (fn 5, above), p.6: "*Experts also discussed the degree of change that should be considered an alteration according to the Directives, given the plasticity of genomes and the genetic variation that occurs naturally and through traditional breeding techniques. A minority of experts considered a single base pair change was sufficient to be captured by the legislation*". NTWG p.9: "*a majority of experts consider that if the 'foreign' genetic material is present but is not able to replicate the organisms should not be considered a GMO. A minority of experts agreed that as long as this 'foreign' genetic material is present even if it's not able to replicate the organism should be considered a GMO*". NTWG, p.13: "*There are two possible interpretations about the coverage of ODM by the GMO legislation...: ODM is not captured by Annex I A Part 1 on the grounds that oligonucleotides introduced into the cell are not recombinant nucleic acid molecules capable of continued propagation (No.1) and they are not heritable material (No.2). Furthermore, the resulting organisms from ODM are captured by Annex IB because the technique entails mutagenesis... This represents the view of a majority of experts. ODM is similar to the techniques listed in Annex I A, Part 1, because ODM is a recombinant nucleic acid technique that (i) leads to a new combination of genetic material resulting in a heritable change in the DNA sequence.. and (ii) it involves the direct introduction of heritable material prepared outside the organism.. This represents the view of a minority of experts*".

2001/18 and that this exemption also applies to a mutagenesis with the help of new techniques which leads to comparable results. However, such an exemption is not admissible, as the risks which stem from the new techniques of ODM (RTDS) techniques, were, until now, not exhaustively examined, are not necessarily known and as the ODM techniques do not have a long safety record.

II.4 Answer to Question II

(87) The answer to question 2 is therefore, that the Decisions by BVL did not take into the consideration the objective and purpose of Directive 2001/18, as expressed in Recital 17 of that Directive. They are therefore not in compliance with the requirements of Directive 2001/18.

III. Answer to the two questions raised

(88) 1. The breeding techniques which use oligonucleotides for genetic modification as well as those which recur to CRISPR/Cas techniques are covered by Directive 2001/18/EC

2. The Decisions by the German Bundesamt für Verbraucherschutz und Lebensmittelsicherheit of 5 February 2015 and 1 June 2015 on RTDS oilseed rape did not take into consideration the objective and purpose of Directive 2001/18/EC. They are not in compliance with the requirements of that Directive.

Ludwig Krämer

September 2015