

**Legal Analysis of the applicability of
Directive 2001/18/EC on genome editing technologies**

**commissioned by the
German Federal Agency for Nature Conservation**

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October 2015

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I. Object of study

In the past few years, different procedures regarding genome editing led to a revolutionary development of genetic engineering. In 2011, genome editing was chosen by Nature Methods as the Method of the Year.¹ These procedures that are generally labeled as "new technologies" and described in greater detail in the following section not only open fascinating perspectives for the modification of genomes but are also considered to bear significant risk potentials. Today, they are foreseeable only to some degree due to the novelty of the procedures and the lack of relevant studies.

The legal assessment of these new technologies is highly controversial. Whereas some voices consider Directive 2001/18/EC to be applicable, various other stakeholders such as the German Federal Office of Consumer Protection and Food Safety (Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, BVL) or the Working Group on New Technologies argue that the new technologies should be excluded from the scope of Directive 2001/18/EC. The present expert opinion is aimed at clarifying this question. The response can in fact be considered as a strategic direction for the entire future development of European law on genetic engineering.

The procedures of genome editing that are considered in this expert opinion are generally summarized under the term 'new technologies'. They include, in particular, the Zinc Finger

¹ Method of the Year 2011. Nat Meth 9 (1), 1-1.

Nucleas Technology (ZFN), the Oligonucleotide Directed Mutagenesis (ODM), the Transcription Activator-Like Effector Nucleases (TALENs) and the use of Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR):

"As early as 1996, a zinc finger protein domain coupled with the FokI endonuclease domain was demonstrated for the first time to act as a site-specific nuclease cutting DNA at strictly defined sites in vitro. This chimeric protein has a modular structure, because each zinc finger domain recognizes one nucleotide triplet (zinc finger nuclease, ZFN). This method became the basis for editing cultured cells, including pluripotent stem cells, plant and animal models [3-8]. However, the ZFN-based technology has a number of disadvantages, including the complexity and high cost of protein domains construction for each particular genome locus and the probability of inaccurate cleavage of target DNA due to single nucleotide substitutions or inappropriate interaction between domains. Therefore, an active search for new methods for genome editing was continued. In recent years, this search has led to the development of new tools for genome editing: TALENs (transcription activator-like effector nucleases) and CRISPR/Cas9 (clustered regulatory interspaced short palindromic repeats). These systems are characterized by a relative construction simplicity and a high functional efficiency in human, animal, and plant cells. These systems, which are extensively used for various genome manipulations, allow one to solve complex problems, including the mutant and transgenic plants and animals generation, development and investigation of disease models based on cultured human pluripotent cells. Furthermore, chimeric proteins based on the TALE and inactivated Cas9 nuclease DNA-binding domains were used in experiments on the regulation of

gene transcription and for studying the epigenomes and behavior of chromosomal loci in the cell cycle.”²

The CRISPR/Cas9 is generally seen as “unique and flexible owing to its dependence on RNA as the moiety that targets the nuclease to a desired DNA sequence. In contrast to ZFN and TALEN methods, which use protein-DNA interactions for targeting, RNA-guided nucleases (RGNs) use simple, base-pairing rules between an engineered RNA and the target DNA site.”³

Also, the Oligonucleotide Directed Mutagenesis (ODM)⁴ is generally known as a very effective method to create single nucleotide changes in a gene.⁵ Whereas classical methods for specific modification purposes of characteristics can only lead to un-directed mutagenesis whose impact and effects are not foreseeable on a genetic level, the use of Oligonucleotide Directed Mutagenesis is a tool for targeted mutagenesis, i.e. it makes the production of numerous mutants and the subsequent identification of desired effects redundant.⁶

² Nemudryi/Valetdinova/Medvedev/Zakian, TALEN and CRISPR/Cas Genome Editing Systems: Tools of Discovery, Acta Naturae. 2014 Jul-Sep; 6(3): 19-40.

³ Sander/Joung, CRISPR-Cas systems for editing, regulating and targeting genomes, Nature Biotechnology 32, 347-355 (2014).

⁴ The so-called RTDS™ (Rapid Trait Development System) represents a variant of the ODM; see Stellungnahme der Zentralen Kommission für die biologische Sicherheit, June 2012.

⁵ Trevan/Boffey/Goulding/Stanbury, Biotechnologie - Die biologischen Grundlagen, 2013, p. 177.

⁶ Munk, Taschenlehrbuch Biologie: Genetik, 2010, p. 401.

ODM is a base pair-specific oligonucleotide-directed gene editing platform. The basic requirement for the application of this technique is that the nucleotide sequence of the gene is known. This is generally the case whenever the product of the respective gene is characterized sufficiently to undergo modifications.⁷ To direct the targeted gene, a chemically synthesized oligonucleotide is designed to create mismatched base pairs, and introduced in the wildtype organism. The introduced oligonucleotide "hybridizes at the target region and the mismatched base pairs work to direct the cell's repair system at those sites to correct (replace, insert, or delete) the designated base(s). [...] This technique has been successfully deployed in bacterial, fungal, mammalian, and plant systems."⁸.

The technique of Oligonucleotide Directed Mutagenesis has the potential to produce new proteins. Studies on Tyrosyl-tRNA-synthetase (TyrTS) as a prototype enzyme have shown that there are prospects "to 'tune' already existing enzymes via ODM, with regard to affinity, catalytic velocity constant, optimum temperature, pH optimum etc."⁹ However, mutated forms are under certain conditions less active than the wild type.¹⁰

⁷ Trevan/Boffey/Goulding/Stanbury, *Biotechnologie - Die biologischen Grundlagen*, 2013, p. 177.

⁸ Gocal/Schöpke/Beetham, *Oligo-Mediated Targeted Gene Editing*, in Zhang/Puchta/Thomson (Eds.), *Advances in New Technology for Targeted Modification of Plant Genomes*, 2015, p. 73.

⁹ Trevan/Boffey/Goulding/Stanbury, *Biotechnologie - Die biologischen Grundlagen*, 2013, p. 179.

¹⁰ Trevan/Boffey/Goulding/Stanbury, *Biotechnologie - Die biologischen Grundlagen*, 2013, p. 178 et seq.

II. Regulatory Framework

The relevant regulatory framework for the legal assessment of the techniques described above is "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/EEC".¹¹ Initial points of further consideration are mainly the specifications of Articles 1 to 3 which read as follows:

"Article 1 - Objective

In accordance with the precautionary principle, the objective of this Directive is to approximate the laws, regulations and administrative provisions of the Member States and to protect human health and the environment when:

- carrying out the deliberate release into the environment of genetically modified organisms for any other purposes than placing on the market within the Community,

¹¹ A general overview is provided by Francescon, *The New Directive 2001/18/EC on the Deliberate Release of Genetically Modified Organisms into the Environment: Changes and Perspectives*, *Review of European Community & International Environmental Law*, Volume 10 (2001), Issue 3, 309-320, DOI: 10.1111/1467-9388.00290; Garcia, *Directive 2001 /18/EC on the Deliberate Release into the Environment of GMOs: an Overview and the Main Provisions for Placing on the Market*, *Journal for European Environmental & Planning Law*, Volume 3 (2006), Issue 1, 3 - 12, DOI: 10.1163/187601006X00029

- placing on the market genetically modified organisms as or in products within the Community.

Article 2- Definitions

For the purposes of this Directive:

(1) "organism" means any biological entity capable of replication or of transferring genetic material;

(2) "genetically modified organism (GMO)" means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;

Within the terms of this definition:

(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) (...)

Article 3 - Exemptions

1. This Directive shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B.

2. (...)”

Of essential importance regarding the regulatory embodiment are therefore the annexes of the directive that determine:

“Annex IA

Techniques referred to in Article 2(2)

Part 1

Techniques of genetic modification referred to in Article 2(2) (a) are inter alia:

(1) recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside an organism, into any virus, bacterial plasmid or other vector system and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation;

(2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;

(3) cell fusion (including protoplast fusion) or hybridisation techniques where live cells with new combinations of heritable genetic material are formed through the fusion of two or more cells by means of methods that do not occur naturally.

Part 2

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

(1) in vitro fertilisation,

(2) natural processes such as: conjugation, transduction, transformation,

(3) polyploidy induction.

Annex I B

Techniques referred to in Article 3

Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are:

(1) mutagenesis,

(2) cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding methods.”

III. Legal assessment

The legal assessment of the technologies in question relies on the framework of European law, more precisely, Directive 2001/18/EC - being part of one of the most comprehensive and advanced GMO-related regulations in the world.¹² Directives are, as commonly known, legal acts that need to be transposed and they thus offer the opportunity to examine closely national laws, too. However, given the obligation of Member States to union-friendly behavior and to interpret transposed legislation in conformity with the directive (general primacy of European law), this approach would not lead to new insights. Therefore, the starting point for the following discussion is European secondary law on deliberate release.

1. The term „genetically modified organism“

Of central importance for the legal assessment is the question if the organisms that are produced by these new technologies are genetically modified in the sense of Directive 2001/18/EC or not. The Directive itself does not provide a conclusive

¹² Husby, A general introduction to the regulation of GMOs and gene technology, in: Traavik/Lim (Eds.), Biosafety First, 2007, chapter 22, p. 6.

definition. Even though Article 2 No. 2 of the Directive provides one of "genetically modified organism" (GMO), the reference to Annex I A Part 1 and Annex I A Part 2 leaves substantial room for interpretation.

The reason for the non-conclusive character of the definition in Article 2 No. 2 is primarily that in Annex I A Part 1 which deals with the techniques of genetic modifications referred to in Article 2 (2) (a) does not enumerate the mentioned techniques in a conclusive manner and only lists examples ("inter alia"). Furthermore, Annex I A Part 1 does not concretize the techniques that are referred to. This makes it necessary to clarify what standard of knowledge the European legislator had at the time of the adoption of Directive 2001/18/EC.

A similar need for clarification arises with regard to Annex I B that applies to the techniques referred to in Article 3 which are excluded from the scope of the Directive. Here, the technique respectively the method of mutagenesis is named but there are no further explanations with regard to the legislator's specific understanding of the term.

Due to this lack of additional explanations, the previously outlined questions need to be clarified by carefully and globally interpreting the Directive's wording. In addition, the literal interpretation has to be seen within its historical, systematic and teleological context.

a. Annex I A Part 1 No. 1: insertion of nucleic acid molecules

The term of the insertion of nucleic acid molecules is not further explained in the Directive. Therefore, the understanding of the term by the European legislator at the time of its adoption remains unclear. As commonly known, Directive 2001/18/EC replaced the deliberate release regime of Directive 90/220/EC. The process of transformation can thus deliver important insights. Further indications are also provided in the Report of the Commission on the Review of Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms (4), adopted on 10 December 1996 and named in recital 1 of the Directive 2001/18/EC. According to Recital 1 of Directive 2001/18/EC, this report identifies a number of areas where improvement is needed.

aa. Literal interpretation

According to the well-established principle of legal interpretation, firstly, a literal analysis dedicated to the general understanding of the term is necessary. The Directive refers to "insertion of nucleic acid molecule (...) capable of continued propagation" in a very general manner without any further specification. There are neither narrowing criteria regarding the ability of reproduction nor any other insertions that would allow a narrow comprehension. From a literal interpretation point of view of Annex I A Part 1 No. 1, it can only be concluded that simply any form of insertion of nucleic acid molecule capable of continued propagation leads to an application of the deliberate release regime of Directive 2001/18/EC.

Furthermore, current technical discussions about the term of the ability of reproduction do not conflict with this view. On the contrary, considering the fact that the restriction of the ability of reproduction of nucleic acid molecules is highly controversially discussed among scientists,¹³ from a legal perspective, a use of the term as widely as possible has to be assumed.

bb. Historic dimension

The fact that according to Annex I A Part 1 No. 1, "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" does not oppose this evaluation. Annex I A was drafted at a time where the vector-free transformation for the purpose of a broad application in the area of genetic engineering was not available:

Even though extensive research on ZFN, as previously mentioned, was already conducted in 1996, it revealed a whole bunch of immense disadvantages, including the complexity and high cost of protein domains construction for each particular genome locus and the probability of inaccurate cleavage of target DNA due to single nucleotide substitutions or inappropriate interaction between domains.¹⁴ ZFN therefore never

¹³ This fact is, inter alia, also highlighted by the Final Report of the New Techniques Working Group.

¹⁴ Nemudryi/Valetdinova/Medvedev/Zakian, TALEN and CRISPR/Cas Genome Editing Systems: Tools of Discovery, *Acta Naturae*. 2014 Jul-Sep; 6(3): 19-40.

played a noteworthy role in daily work with plant genetics which could have raised the European legislator's attention. Whereas TALENs was discussed in a considerable extent for the first time in 2011, CRISPR/Cas9 has been relevant in the scientific discourse only since 2013.¹⁵ For purely practical reasons, the European legislator was therefore not able to deal with these new techniques in the 1990s.

cc. Systematic considerations

This result is additionally supported by the fact that Annex I A Part 1 enumerates the techniques of genetic modification named in No. 1 to 3 and referred to in Article 2 (2) (a) only in the sense of an indicative list. By use of an 'inter alia' approach, the European legislator made sure that techniques that were unknown or not commonly established at the time of the adoption of the Directive can now fall within its scope. As indicative lists are commonly used in numerous national laws and namely also in European law¹⁶, further explanations regarding the legal impact are not necessary. Nevertheless, it should be mentioned that the use of the inter alia approach can be traced back to a demand of the Commission. In its "Report on the Review of Directive 90/220/EEC in the Context of the Commission's Communication on Biotechnology and the White

¹⁵ Nemudryi/Valetdinova/Medvedev/Zakian, TALEN and CRISPR/Cas Genome Editing Systems: Tools of Discovery, *Acta Naturae*. 2014 Jul-Sep; 6(3): 19-40.

¹⁶ See Art. 6 para 2 Directive 98/44/EC (regarding patentability of biotechnological inventions).

Paper"¹⁷, the Commission refers to Part D and the annexes of Directive 90/220/EEC and makes the following statement: "The flexibility of the Directive appears to be limited as it does not provide for easy adaption to technical progress of one of its Technical Annexes. In a so fast-moving and continually evolving field, it is important to ensure that Community provisions are always based on the latest stage of experience and scientific knowledge. Therefore, the possibility of adapting all annexes of the Directive through a Regulatory Committee Procedure, could enhance flexibility and permit timely adaption of these highly technical parts of the Directive to rapidly advancing scientific and technical progress."¹⁸

Admittedly, the Commission was not able to enforce its demand for the establishment of a Regulatory Committee Procedure but its demand for a flexible use of the annexes was taken into account in form of an "inter alia" solution. The inter alia approach adopted in Directive 2001/18/EC provides thus the opportunity to cover new techniques within the scope of Annex I A Part 1.

Significantly, the European legislator adopted this approach in Annex I A Part 1 but not in Annex I B. As a result, a dynamic application of the annexes, i.e. an application that is also reflecting the latest technical developments is only possible in so far as the applicability of Directive 2001/18/EC

¹⁷ Report on the Review of Directive 90/220/EEC in the Context of the Commission's Communication on Biotechnology and the White Paper, dated 10.12.1996, COM(96) 630 final.

¹⁸ P. 10 of the report.

is in question. This means that the possibility of a flexible application of the exceptions of the Directive's scope which are aimed at by Annex I B shall be excluded. It is undisputed that this represents an exhaustive list.¹⁹

dd. Teleological considerations

Finally, the teleological perspective, i.e. the question of what has been intended by the specifications of Annex I A Part 1 No. 1 also needs to be taken into account. In this context, the European legislator's basic philosophy of regulation is of utmost importance and will be considered in more detail below.²⁰ In addition, Annex I A Part 1 No. 1 also delivers important hints. According to this clause, the incorporation into a host organism is relevant in which the nucleic acid molecules do not naturally occur. The key issue for the European legislator is thus the fact that the use of the respective techniques leads to a result which does not correspond to the natural state. But regarding the techniques in question, this is undoubtedly the case.

The fact that mutations as such [sic!] can indeed occur naturally is irrelevant in this context. Instead, it is crucial for the conclusion that the 'not natural appearance' has not been assessed in a general-abstract but in a individual-concrete way. Annex I A Part 1 explicitly states that the technique in question leads to the incorporation into a host

¹⁹ New Techniques Working Group, Final Report, p. 3.

²⁰ See IV 2 and 3.

organism in which the nucleic acid molecules do not naturally occur. This clause contains several legal aspects.

First of all, Annex I A Part 1 No. 1 essentially refers to the procedure of incorporation. From an applicability point of view, it is sufficient that an incorporation as such is performed. The fact that this organism can in turn be reproduced without any further incorporation is irrelevant.

This view is furthermore supported by the fact that Annex I A Part 1 No. 1 merely requires the modification of "a" host organism. Here, it is also irrelevant what happens to the host organism afterwards. The only requirement for the purpose of application of Annex I A Part 1 No. 1 is that the respecting nucleic acid molecules do not occur naturally in the respecting host organism.

To sum up, in terms of applicability of Annex I A Part 1 No. 1 it is important if a) the concrete modification in question b) within the respecting organism c) occurs naturally or not.

This is not the case with regard to the modifications caused by ODM or similar new techniques. Instead, organisms are modified in a targeted way that would otherwise definitely not have occurred in the concrete organism. As a targeted point mutation is involved, Annex I A Part 1 No. 1 (in contrast to the opinion of, for instance, the Central Commission for bio-

logical Safety in Germany)²¹ has to be applied to ODM and similar techniques.

ee. Aspects of a possible cumulative application

In addition, when assessing new techniques it has to be taken into account that the respective procedures can be applied one after another with the effect that in the end, extensive modifications up to the substitution of the whole genome of the target organism can be reached. This raises the question of the legal relevance of such kind of 'series' of single applications.

Initially, it cannot be criticized per se that individuals or businesses develop these techniques further by use of legislative margins in a way that particular statutory restrictions cannot be applied. Only in cases in which such an approach would turn out to violate concrete rights such as the circumvention of standards of protection (especially if the damage of a third party is intended) leads to a violation of existing laws.

However, the described possibility of an application of different procedures does not have to be dealt with because it could be seen as an intended circumvention of the requirements of Directive 2001/18/EC. The mentioned possibility is rather relevant from a different aspect, i.e. from the ratio of Annex I A Part 1 No. 1. It has already been made clear that Annex I

²¹ Stellungnahme der Zentralen Kommission für die biologische Sicherheit, June 2012.

A Part 1 No. 1 can be applied to the singular use of relevant techniques. Thus, "a maiore ad minus", this clause is applicable considering the possibility of an 'exponentiated' application of the relevant technologies.

b. Annex I A Part 1 No. 2: heritable material

As previously mentioned, the entire enumeration in Annex I A Part 1 represents an indicative list and the techniques in question fall under the range of the alternative of Annex I A Part 1 No. 1 so that there is no doubt with regard to the scope of application of the Directive.²²

However, for the sake of completeness, it has to be clarified whether or not the relevant techniques can also fall under the range of Annex I A Part 1 No. 2. This requires a procedure involving the direct introduction into an organism of heritable material prepared outside the organism. The considerations regarding this matter made by the New Techniques Working Group tend to contradict an according qualification of these techniques:

„The term heritable material is used in Annex IA, Part 1(2) and Part 1(3) of Directive 2001/18/EC and Annex I, Part A(2) and Part A(3) of Directive 2009/41/EC. In both instances the term is used in the context of genetic material, which, when introduced directly (i.e. without the involvement of a vector system) into an organism (micro-organism) by procedures including micro-injection, micro-encapsulation or cell fusion,

²² See IV 1 a.

will result in a "technique of genetic modification" in the sense of the Directives. Although heritable material is not clearly defined in the Directive, there are two possible interpretations:

i. "heritable material" must be inherited in the case in question. The argument being that the first indent in the list of Annex IA Part 1²³ involves the use of vectors and refers to the transfer of genetic material into a host organism and continued propagation. In order for this to be consistent with the second indent in the list of Annex IA Part 1²⁴ heritable material should be interpreted as being propagated through the host organism and not just being transiently present (see section 4.4); and,

ii. "heritable material" has simply to be capable of being inherited. GMOs that have been authorised to date, and into which 'heritable material prepared outside of the organism' has been introduced directly, have in all cases been capable of passing this material onto their offspring. Whereas, nucleic acid introduced into cells using some of these new tech-

²³ "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 the 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".

²⁴ "techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation".

niques will not be inherited e.g. in the case of ODM, ZFN-1 ZFN-2 and RNA-dependent DNA methylation. However, the changes they impart will be inherited (although this is limited in the case of RNA-dependent DNA methylation)."²⁵

However, on the one hand, one can argue against the definition of "heritable material" as „to be inherited in the case in question" that in Annex I A Part 1 No. 2 the listed techniques of micro-injection, macro-injection and micro-encapsulation are listed only as examples ("including"). On the other hand, it is possible to incorporate the heritable genetic material not only directly but also indirectly through a vector system.²⁶ For this reason alone, the attempt of the New Techniques Working Group to differentiate between Annex I A Part 1 No. 1 and Annex I A Part. 1 No. 2 is not convincing.

In addition, the wording of Annex I A Part 1 No. 2 does not require concrete inheritance of the respective genetic material but capacity of inheritance and therefore some 'basic potential' of inheritance. This is not only illustrated by the German official translation of Directive 2001/18/EC which merely refers to "Einführung von Erbgut in einen Organismus" but by the English version of the Directive: the sole qualification of the material as inheritable does not imply that this potential must come to light at a certain point in time or in a certain manifestation.

²⁵ P. 7 of the Report.

²⁶ https://en.wikipedia.org/wiki/Genetic_engineering [02.10.2015] shall be regarded as sufficient evidence.

Furthermore, it can be referred to the need to interpret Annex I A Part 1 No. 2 in light of the intention of the European legislator who, by the means of a process-oriented approach²⁷, wanted a simple use of genetic techniques to suffice for opening the scope of application of Directive 2001/18/EC. Additionally, it needs to be pointed out that all techniques mentioned in Annex I A Part 1 are part of an indicative list only so that especially the development of new technologies is covered by Annex I A Part 1.

Overall, most convincing are the arguments which support the view that the new techniques are not only covered by Annex I A Part 1 No. 1 but also by Annex I A Part 1 No. 2. Therefore, they fall within the scope of application of the Directive in one way or the other.

c. Annex I B: mutagenesis

Annex I B of Directive 2001/18/EC defines certain procedures that, with regard to the European legislator's intention, do not fall within the range of application of the Directive.

aa. 'Rule and exemption' approach

Firstly, one has to consider the relationship between Article 2 of the Directive and Annex I A on the one hand and Article 3 of the Directive and Annex I B on the other hand. The wording of the Directive already implies that Article 2 and the corresponding Annex represents a rule and Article 3 and Annex I B

²⁷ See IV 3.

the exemption. The official title of Article 3 of the Directive therefore reads "Exemptions". Only this reading satisfies the purpose of the Directive, i.e. in particular the realization of the precautionary principle, as it is described in Article 1 of Directive 2001/18/EC:

"In accordance with the precautionary principle, the objective of this Directive is to approximate the laws, regulations and administrative provisions of the Member States and to protect human health and the environment when:

- carrying out the deliberate release into the environment of genetically modified organisms for any other purposes than placing on the market within the Community,
- placing on the market genetically modified organisms as or in products within the Community."

This legislator's decision of a 'rule and exemption' approach is of extraordinary importance because the exemptions need to meet very strict application criteria at all times. Thus, the assumption of an exception by way of mere analogies is not convincing.

bb. Restriction to conventional mutagenesis

It has to be said that the term mutagenesis is, at first sight, comparatively open and includes ultimately any production of mutations in the genome of living organisms. But it needs to be differentiated between conventional and site-directed mutagenesis. It is widely undisputed that besides ge-

netically modified organisms and conventionally cultured organisms, organisms won via mutagenesis form an independent third category due to aspects of risk evaluation.²⁸ This category not only refers to the conventional procedure of mutagenesis but also to any other procedure in which the cultured organisms are exposed to mutagenic, i.e. the genome modifying conditions (above all radiation or chemical substances) with defined mutagenicity.²⁹ These methods of mutations have been used for the past 100 years and therefore have a comparatively long "safety record".

Annex I B of Directive 2001/18/EC has to be interpreted in light of this conventional mutagenesis due to both the repeatedly mentioned purpose of the Directive respectively its underlying 'philosophy of regulation' and the recitals. Even though the recitals are as such not legally binding components of the Directive, their underlying ideas of the European legislator nevertheless develop legal relevance. The recitals represent thus an interpretation aid that can not only be used in the course of the interpretation of the norms but are also supposed to be used.

cc. In particular: recital 17

Recital 17 is of utmost importance with regard to the leading question. The legal provision affects Annex I B and reads as

²⁸ Cf. Peterson/Shama, A comparative risk assessment of genetically engineered, mutagenic, and conventional wheat production systems, *Transgenic Res.* 2005 Dec;14(6):859-75.

²⁹ Morot-Gaudry/Lea/Briat, *Functional Plant Genomics*, 2007, p. 145.

follows: „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.“ Herein, it is unambiguously clarified that merely conventional techniques are excluded from the range of Directive 2001/18/EC and only given the additional requirement that a long safety record for this conventional technique exists.³⁰ In case of the ODM technique and related new techniques, both requirements are not met. The ODM technique is rather a completely different and new technique for which no relevant empirical value exists.

In this context, it is of peculiar interest that the proponents of an exclusion of new techniques from the range of Directive 2001/18/EC regularly refer to high security risks if the same technique was used in the human system. Thus, the Deutsche Akademie der Naturforscher Leopoldina e.V., the Deutsche Forschungsgemeinschaft, the acatech - Deutsche Akademie der Technikwissenschaften e.V., and the Union der deutschen Akademien der Wissenschaften e.V. elucidate in a new joint statement the following:

“However, before the technique can be used in medical applications, there are several challenges to overcome. First, the basic molecular mechanisms of the CRISPR-Cas9 system must be explored further. Moreover, there must be an increase in effi-

³⁰ See also Dunlop, *GMOs and regulatory styles*, in: *Environmental Politics*, Volume 9, Issue 2, 2000, DOI:10.1080/09644010008414528; Husby, *A general introduction to the regulation of GMOs and gene technology*, in: *Traavik/Lim (Eds.), Biosafety First*, 2007, chapter 22, p. 8.

ciency, selectivity and safety, so that only the specifically desired cell types are genetically modified, and unintended mutations elsewhere in the genome (off-target mutations) are prevented. There is still a significant lack of the necessary insight into the complex interplay between human genes and/or individual gene variants and of genome-wide knowledge about the functioning of the chromatin that packages the DNA. It is at this epigenetic level that decisions are made on whether, and to what extent, a particular gene is activated or inhibited. Scientists are only just beginning to gain a rudimentary understanding of chromatin, which is also significantly influenced by environmental factors. That means that they are not yet able to reliably predict the long-term consequences of even simple genetic changes. Interestingly, CRISPR-Cas9 is becoming a key technology in this area too, as it has enabled scientists to influence the epigenome in a targeted way for the first time²⁴ and has placed completely new possibilities at the fingertips of epigeneticists."³¹

In addition, possible threats to the ecological system are openly addressed: "Alongside the scientific dialogue that has already begun, there should be public debate on the scientific, ethical and legal possibilities of genome editing and on its limits and consequences, particularly with regard to therapeutic applications and to targeted, potentially far-reaching interventions in ecosystems. It is important to have

³¹ Deutsche Akademie der Naturforscher Leopoldina e.V./Deutsche Forschungsgemeinschaft/acatech - Deutsche Akademie der Technikwissenschaften e.V./Union der deutschen Akademien der Wissenschaften e.V. (Eds.), The opportunities and limits of genome editing, Statement, September 2015, p. 25.

an objective debate that informs all stakeholders in a clear and transparent manner about the status of research and development into the techniques, and to ensure that any decisions taken are based on sound scientific evidence. The techniques should be studied and improved further [...]."³²

Thus, it cannot be assumed that the new techniques do not (and not even to some extent) meet the criteria of a sufficient safety record. In contrast, there is a high number of security specific questions that need to be addressed in a satisfactory manner in the next few years and decades.

The term mutagenesis refers in terms of Annex I B explicitly only to conventional procedures of mutagenesis but not to procedures of the site-directed mutagenesis. Thus, the statement of the New Techniques Working Group regarding Annex I B has to be seen very critically. The statement reads as follows:

"The term "recombinant nucleic acid molecules" is used in Annex IB of Directive 2001/18/EC and Annex II Part A of Directive 2009/41/EC. In line with the aforementioned Directives, a recombinant nucleic acid molecule is created outside the cells through the formation of a new combination of genetic material/nucleic acid molecules. There was a discussion on how many nucleotides could constitute a new combination of genetic material/nucleic acid molecules in this context. A ma-

³² Deutsche Akademie der Naturforscher Leopoldina e.V./Deutsche Forschungsgemeinschaft/acatech - Deutsche Akademie der Technikwissenschaften e.V./Union der deutschen Akademien der Wissenschaften e.V. (Eds.), The opportunities and limits of genome editing, Statement, September 2015, p. 27.

majority of experts concluded that in order to form a new combination, a nucleotide sequence of at least 20 bp 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."³³

Additionally, the statement points out the "similarities" of the respective techniques to conventional mutagenesis:

"Similarity to mutagenesis:

- Oligonucleotide-directed mutagenesis (ODM) is a form of mutagenesis induced by oligonucleotides.
- Only oligonucleotides with sequence similarity or analogy to the recipient's genome are used (they may be modified chemically to improve stability).
- During the application of ODM, modifications are made to the organism's genetic material by the hosts own repair mechanisms.
- The induced point mutations are site-specific. Similar mutations can occur spontaneously in nature or may be induced by conventional mutagenesis (chemical or radiation)."³⁴

Regarding these explanations, it needs to be pointed out that an indication for a restriction to a certain minimum number of nucleotides cannot be found in Directive 2001/18/EC. Even if such a minimum number is assumed, this would not result in the

³³ P. 6 of the Report.

³⁴ P. 12 of the Report.

applicability of Annex I B but in its non-applicability and therefore in the applicability of Directive 2001/18/EC.

Above all, the statements of the New Techniques Working Group regarding the "similarity" of the ODM technique and conventional mutagenesis prove themselves to be incorrect. It is - as already demonstrated - especially in light of recital 17 clear that only conventional mutagenesis procedures are excluded from the applicability of Directive 2001/18/EC. Additionally, the rule and exemption approach in Article 2 and Article 3 respectively in Annex I A and Annex I B, as discussed earlier, contradicts an admissibility of such analogies. The assumptions of the New Techniques Working Group are therefore - at least from a legal point of view - clearly incompatible with the requirements of Directive 2001/18/EC.

dd. Legislative discussions during the adoption of Directive 2001/18/EC

The previous results are supported to their full extent by a historic analysis of Directive 2001/18/EC. It can be regarded as generally recognized that Directive 2001/18/EC did not intend a basal reorientation of the understanding of the term which is of interest here.³⁵

With regard to the leading question it becomes apparent that Article 2 and 3 of Directive 2001/18/EC basically adopt the

³⁵ See Palme, in: Eberbach/Lange/Ronellenfitsch (Eds.), Recht der Gentechnik und Biomedizin, 88th supplement, March 2015, Part I, D. II, marginal no. 16.

wording of the previous regulations in Directive 90/220/EEC (Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms³⁶). The only changes that were made by the legislator affect aspects which are of no importance for the leading question. On the one hand, a clarification was added to Article 2 (2) of Directive 2001/18/EC with regard to the possibilities of somatic genetic therapy, according to which a human being does not represent a GMO. On the other hand, a second paragraph was added to Article 3 of Directive 2001/18/EC which stipulates an exemption clause for aspects regarding transport.

However, many relevant extensions can be found in the annexes of Directive 2001/18/EC compared to the original version of Directive 90/220/EEC. The original Directive 90/220/EC reads as follows:

„Annex I A

Techniques referred to in Article 2 (2)

Part 1

Techniques of genetic modification referred to in Article 2 (2) (i) are inter alia:

(1) recombinant DNA techniques using vector systems as previously covered by Council Recommendation 82/472/EEC (;); (...)

³⁶ OJ L 117, 8.5.1990, p. 15-27.

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, (...)."

As a result of the revised version on the deliberate release directive, the following changes were made regarding the parts that are herein of interest. On the one hand, Annex I A Part 1 lists as techniques of genetic modification all 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.

On the other hand, Annex I B is dedicated to the exemptions of the applicability of the Directive in such a manner that techniques/methods of genetic modification yielding organisms are to be excluded from the Directive in a way 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. The term mutagenesis was however understood precisely in the same way in which it is now (and still) used in the context of European law on deliberate release.

ee. Interim result

As an interim result, it can be noted that the new techniques represent procedures in terms of Article 2 (2) No. 2 combined with Annex I A Part 1 No. 1 of Directive 2001/18/EC. In contrast, it is impossible to imagine any aspect under which the respective techniques can be assigned to the range of Article 3 combined with Annex I B.

2. Significance of the precautionary principle

Although the legal evaluation of the respective new techniques seems clear due to the interpretation in the light of the above discussed articles, for the sake of completeness, further considerations which undermine the accuracy of the previous results shall be taken into account.

a. In general: precautionary principle in law on the deliberate release of genetically modified organisms

In this context, the precautionary principle plays a pivotal role. It is common knowledge that the precautionary principle is of crucial importance with regard to the entire European environmental law. In addition, the European Union has urged to establish this principle on an international level during the negotiations regarding the Biosafety Protocol.

In the meantime, the precautionary principle has been established within the primary law of the European Union. Article 191 (2) of the Treaty on the Functioning of the European Union

states as follows: "Union policy on the environment shall aim at a high level of protection taking into account the diversity of situations in the various regions of the Union. It shall be based on the precautionary principle and on the principles that preventive action should be taken, that environmental damage should as a priority be rectified at source and that the polluter should pay."

Thus, the precautionary principle outlines a defining guiding principle of the European environmental law and is explicitly included in the law on deliberate release. Even though Directive 90/220/EEC did not refer to the precautionary principle, the European Court of Justice has ruled that the validity of this principle needs to be ensured in the implementation of Directive 90/220/EEC.³⁷

However, in contrast to Directive 90/220/EEC, a clarification by the European Court of Justice with regard to Directive 2001/18/EC is not necessary. Recital 6 of Directive 2001/18/EC states that "[u]nder the Treaty, action by the Community relating to the environment should be based on the principle that preventive action should be taken." Especially recital 8 emphasizes the importance of this principle with regard to the transformation of the Directive. "The precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it."

³⁷ Cf. European Court of Justice, Case C-6/99 - Association Greenpeace France and Others v. Ministère de l'Agriculture et de la Pêche and Others (2000), ECR I-6031, para 41 and next.

Finally, within the legally binding part of Directive 2001/18/EC, Article 1 clarifies that the precautionary principle represents a key criterion in the law on deliberate release:

"In accordance with the precautionary principle, the objective of this Directive is to approximate the laws, regulations and administrative provisions of the Member States and to protect human health and the environment when:

- carrying out the deliberate release into the environment of genetically modified organisms for any other purposes than placing on the market within the Community,
- placing on the market genetically modified organisms as or in products within the Community."

Basically, the entire Directive 2001/18/EC illustrates a concretization of the precautionary principle, especially within the area of "green genetic technologies".³⁸

b. Specifically: legal content of the precautionary principle

Even if the precautionary principle is laid down not only in primary but also in secondary law this does not affect the

³⁸ Husby, A general introduction to the regulation of GMOs and gene technology, in: Traavik/Lim (Eds.), *Biosafety First*, 2007, chapter 22, p. 8; Herdegen, in: Herdegen (Ed.), *Internationale Praxis Gentechnikrecht*, 89th supplement, July 2015, Directive 2001/18/EC, marginal no. 59.

substantive content of this principle. The generally accepted³⁹ basic lines of European precaution politics are enlisted immaculately in the Communication of the Commission of 2 February 2000 on the precautionary principle⁴⁰. The Commission describes the core content of the precautionary principle as follows: "The precautionary principle enables rapid response in the face of a possible danger to human, animal or plant health, or to protect the environment. In particular, where scientific data do not permit a complete evaluation of the risk, recourse to this principle may, for example, be used to stop distribution or order withdrawal from the market of products likely to be hazardous."⁴¹

Furthermore, the Communication of the Commission guidelines sets out the conditions for the application and concretization of the considered procedures as well as the distribution of the burden of proof. In detail, the Commission determines:

"The precautionary principle is detailed in Article 191 of the Treaty on the Functioning of the European Union (EU). It aims at ensuring a higher level of environmental protection through preventative decision-taking in the case of risk. However, in practice, the scope of this principle is far wider and also covers consumer policy, [European legislation concerning food and human, animal and plant health](#).

³⁹ Palme, in: Eberbach/Lange/Ronellenfisch (Eds.), *Recht der Gentechnik und Biomedizin*, 88th supplement, March 2015, Part I, D. II, marginal no. 24.

⁴⁰ COM(2000) 1 final, <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV:l32042> [03.10.2015].

⁴¹ COM(2000) 1 final, <http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=URISERV:l32042> [03.10.2015].

This Communication establishes common guidelines on the application of the precautionary principle.

The definition of the principle shall also have a positive impact at international level, so as to ensure an appropriate level of environmental and health protection in international negotiations. It has been recognised by various international agreements, notably in the Sanitary and Phytosanitary Agreement (SPS) concluded in the framework of the World Trade Organisation (WTO).

Recourse to the precautionary principle

According to the Commission the precautionary principle may be invoked when a phenomenon, product or process may have a dangerous effect, identified by a scientific and objective evaluation, if this evaluation does not allow the risk to be determined with sufficient certainty.

Recourse to the principle belongs in the general framework of risk analysis (which, besides risk evaluation, includes risk management and risk communication), and more particularly in the context of risk management which corresponds to the decision-making phase.

The Commission stresses that the precautionary principle may only be invoked in the event of a potential risk and that it can never justify arbitrary decisions.

The precautionary principle may only be invoked when the three preliminary conditions are met:

- identification of potentially adverse effects;
- evaluation of the scientific data available;
- the extent of scientific uncertainty.

Precautionary measures

The authorities responsible for risk management may decide to act or not to act, depending on the level of risk. If the risk is high, several categories of measures can be adopted. This may involve proportionate legal acts, financing of research programmes, public information measures, etc.

Common guidelines

The precautionary principle shall be informed by three specific principles:

- the fullest possible scientific evaluation, the determination, as far as possible, of the degree of scientific uncertainty;
- a risk evaluation and an evaluation of the potential consequences of inaction;
- the participation of all interested parties in the study of precautionary measures, once the results of the scientific evaluation and/or the risk evaluation are available.

In addition, the general principles of risk management remain applicable when the precautionary principle is invoked. These are the following five principles:

- proportionality between the measures taken and the chosen level of protection;
- non-discrimination in application of the measures;
- consistency of the measures with similar measures already taken in similar situations or using similar approaches;
- examination of the benefits and costs of action or lack of action;
- review of the measures in the light of scientific developments.

The burden of proof

In most cases, European consumers and the associations which represent them must demonstrate the danger associated with a procedure or a product placed on the market, except for medicines, pesticides and food additives.

However, in the case of an action being taken under the precautionary principle, the producer, manufacturer or importer may be required to prove the absence of danger. This possibility shall be examined on a case-by-case basis. It cannot be extended generally to all products and procedures placed on the market."

c. The impact on the leading question

Given the fact that a sufficient "safety record" which could be comparable to the safety assessment of, for instance, conventional mutagenesis does not exist per definitionem and as the multiple application of one certain technique to the same organism is indeed possible, the range of the precautionary principle allows the applicability of the precautionary measures described by the Commission.

In addition, Article 1 of Directive 2001/18/EC raises the idea of precaution to a key principle of the entire law on deliberate release. Although (as the Communication of the Commission clearly states) random decisions made by the responsible authorities are hence no longer possible, an immediate manifestation of precaution is rather an extensive application of the restriction of Directive 2001/18/EC and, in return, a preferably narrow application of exemption clauses.

The precautionary principle develops an immediate impact on the interpretation of the directive's content and thus strengthens the described⁴² observations regarding the rule and exemption approach of Article 2 and 3 respectively of Annexes I A Part 1 and I B. The concrete implementation of the precautionary principle influences the evaluation of the inter alia approach of Annex I A Part 1 and the understanding regarding the wording of the relevant regulation.

⁴² See IV 1 c aa.

3. Significance of the process approach

The European legislation regarding genetic engineering does not - despite the loosening approaches e.g. through Article 7 of Directive 2001/18/EC - follow a product-oriented but a process-oriented approach.⁴³ Incidentally, this results from the utterly unambiguous wording of Directive 2001/18/EC referring to techniques respectively techniques/methods. In contrast to US law and its defining product-oriented approach, the regulation approach of the European Union is based upon the conviction that even the use of techniques/methods regarding genetic modifications in the process of generating an organism justifies the applicability of the Directive dealing with deliberate release.

⁴³ See, inter alia, Eising/Kohler-Koch (Eds.), *The Transformation of Governance in the European Union*, 2003, p. 73; García, *Directive 2001/18/EC on the Deliberate Release into the Environment of GMOs: an Overview and the Main Provisions for Placing on the Market*, 3 *J. Eur. Envtl. & Plan. L.*, 2006, 3 (5); Lee, *EU Regulation of GMOs: Law and Decision Making for a New Technology*, 2009, p. 196 et seq; Nyman, *New Techniques and the GMO-legislation* (PP), http://www.google.de/url?sa=t&rct=j&q=&esrc=s&source=web&cd=4&ved=0CD0QFjADahUKEwig_PK-sqHIAh-Ah-VI3iwKHY6MDck&url=http%3A%2F%2Fwww.slu.se%2FPageFiles%2F362034%2FMariNyman_140523.pdf&usg=AFQjCNGRwWn12P0mgAXE8qrE5Ia6QyCeUQ ; Jones, *Regulatory uncertainty over genome editing*, *Nature Plants* 2015, 1 (3); Herdegen, in: Herdegen (Ed.), *Internationale Praxis Gentechnikrecht*, 89th supplement, July 2015, Directive 2001/18/EC, marginal no. 68.

Thus, the expressed estimation of the New Techniques Working Group, according to which, for instance, the ODM technique should ultimately not fall under the term GMO of the directive on deliberate release due to a lack of detectability in the final product,⁴⁴ is not convincing. Instead, the fact that techniques regarding genetic modifications are being used for the production of relevant organisms, seen in the light of the process approach gives reason enough to activate the regulation regime of Directive 2001/18/EC.

If or to what extent the process approach is convincing not only from an international comparative law perspective but also from a scientific one and the question if a certain margin for a further development of this approach exists is, at present, of no importance. The fact that the European legislator currently applies the process approach (aside from product specific breaches) is crucial. Directive 2001/18/EC is thus applicable.⁴⁵

4. Relevance of ethical concerns

The legislation of the European Union responds to ethical concerns to a significant extent in the area of regulation regarding genetic engineering and biomedicine. This applies not only to the mandatory labeling of novel food or to the ordre

⁴⁴ P. 12 of the Report.

⁴⁵ See also Herdegen, in: Herdegen (Ed.), *Internationale Praxis Gentechnikrecht*, 89th supplement, July 2015, Directive 2001/18/EC, marginal no. 68 et seq.

public clause of Directive 98/44/EC but also to the scope of application of Directive 2001/18/EC.

In a very general manner, recital 57 of Directive 2001/18/EC refers to the fact that the Commission's European Group on Ethics in Science and New Technologies should be consulted with a view to obtaining advice on ethical issues of a general nature regarding the deliberate release or placing on the market of GMOs. Such consultations should be without prejudice to the competence of Member States as regards ethical issues.

Furthermore, recital 9 emphasizes the commonly approved relevance of ethical considerations and clarifies, in particular, that specific ethical perceptions in individual Member States are generally to be respected. Respect for ethical principles recognized in a Member State is particularly important. Member States may take ethical aspects into consideration when GMOs are deliberately released or placed on the market as or in products.

Article 29 of Directive 2001/18/EC finally leads to an institutionalized ethical review. Based on the Ethics Review Committees known from different contexts, the regulation reads as follows:

"1. Without prejudice to the competence of Member States as regards ethical issues, the Commission shall, on its own initiative or at the request of the European Parliament or the Council, consult any committee it has created with a view to obtaining its advice on the ethical implications of biotechnology, such as the European Group on Ethics in Science and New Technologies, on ethical issues of a general nature. This

consultation may also take place at the request of a Member State.

2. This consultation is conducted under clear rules of openness, transparency and public accessibility. Its outcome shall be accessible to the public.

3. The administrative procedures provided for in this Directive shall not be affected by paragraph 1.”

The described regulations cannot be traced back to the instruments under Directive 90/220/EEC but are incorporated into the law on deliberate release for the first time through Directive 2001/18/EC.⁴⁶ Regardless of the fact that in an international context, open ethical questions have the potential to give rise to conflicts in world trade law,⁴⁷ the European legislator holds on to an extensive support of ethical contemplations. The use of a rather wide ethical concept leads to the result that not only the integration of social discussions or socio-economic considerations but also of scientific critique can influence the decisions of Member States.

This decision of the European legislator is presently not to be evaluated but merely analyzed with regard to the impact that arises for the legal classification of new techniques. It is common knowledge that the opportunities that come along with these new techniques are equally object of broad and very

⁴⁶ See Spranger, *Recht und Bioethik*, 2010, p. 258 et seq.

⁴⁷ Cf. Spranger, *The Ethics and Deliberate Release of GMOs*, *Eubios Journal of Asian and International Bioethics* 11 (2001), 144-146.

detailed discourses⁴⁸ such as decisions of individual national authorities that refer to the admission of respective organisms. Special attention has to be paid to the allegation that the new techniques embody a conscious avoidance of the European law on deliberate release⁴⁹ which leads to a further boost of the current social discussions.

To conclude, the relevant new techniques are currently discussed in a highly controversial manner. Critique regarding these techniques is mostly expressed because the apparent aim to produce "GMOs in camouflage" is reason enough to articulate the described mechanisms of Directive 2001/18/EC.

⁴⁸ See Fontana, Genetically Modified Micro-Organisms: the EU regulatory framework and the new Directive 2009/41/EC on the contained use, *Chemical Engineering Transactions*, 20, 1-6; DOI: 10.3303/CET1020001.

⁴⁹ See Harvey, Genome editing of crops may be restricted by EU rules, warn scientists, *The Guardian*, 21 July 2014, <http://www.theguardian.com/environment/2014/jul/21/genome-editing-crops-restricted-eu-rules-scientists-warn> (03.10.2015); Karberg, Genome Editing umgeht Gentechnik-Gesetz - Natürliche Gentechnik, *Der Tagesspiegel*, 19 February 2015, <http://www.tagesspiegel.de/meinung/genome-editing-umgeht-gentechnik-gesetz-natuerliche-gentechnik/11386596.html> (03.10.2015); Pollack, By "Editing" Plant Genes, Companies Avoid Regulation, *The New York Times*, 1 January 2015, http://www.nytimes.com/2015/01/02/business/energy-environment/a-gray-area-in-regulation-of-genetically-modified-crops.html?_r=0 (03.10.2015); Jones, Regulatory uncertainty over genome editing, *Nature Plants* 2015, 1 et seq.

IV. Summary of the essential results

The organisms produced by so-called new techniques fall under the scope of Annex I A Part 1 No. 1 of Directive 2001/18/EC. This result is based on the analysis of not only the wording and history of the Directive but also on systematic and teleological considerations.

Of particular relevance in this context is the fact that Annex I A Part 1 of Directive 2001/18/EC - in contrast to Annex I B - makes use of the instrument of an indicative list to assure the applicability of the regulatory framework regarding techniques in question.

This extension of Annex I A Part 1 No. 1 corresponds to the explicit intention of the Commission which can be found, in particular, in the "Report on the Review of Directive 90/220/EEC in the Context of the Commission's Communication on Biotechnology and the White Paper".

The fact that mutations as such [sic!] do occur naturally is of no importance in this context. Crucial for this assumption is the fact that the 'not-natural appearance' has to be assessed in a in an individual-concrete but not in a general-abstract way. The modifications caused by ODM and similar new techniques are carried out purposefully and lead to the incorporation into a host organism in which the nucleic acid molecules with certainty do not occur naturally. As this represents a target-oriented point mutation, Annex I A Part 1 No. 1 has to be applied to the relevant genome editing techniques.

Additionally, regarding the techniques in question, it needs to be taken into account that the respective procedures can be applied one after another with the effect that in the end, extensive modifications up to the substitution of the whole genome of the target organism can be reached.

The organisms produced by new technologies fall within the scope of Annex I A Part 1 No. 2 of Directive 2001/18/EC. This interpretation is undermined by the exemplary listing of certain techniques ("including") and the fact that it is possible to incorporate the heritable genetic material not only directly but also indirectly through a vector system.

Furthermore, Annex I A Part 1 No. 2 does not assume a concrete inheritance of the respective genetic material but requires merely the ability of inheritance and therefore the basic potential of inheritance. Finally, it needs to be taken into account that Annex I A Part 1 No. 2 has to be interpreted in light of the aim of the European legislator who intended that the simple use of genetic modifying techniques would be sufficient for the applicability of Directive 2001/18/EC by the means of a process approach.

However, the new techniques cannot be assigned to the term mutagenesis of Annex I B of Directive 2001/18/EC. This evaluation is supported by the rule and exemption approach of Article 2 of the Directive and Annex I A on the one hand and Article 3 of the Directive and Annex I B on the other hand.

Most importantly, it needs to be pointed out that the used term of mutagenesis in Annex I B explicitly covers conventional mutagenesis, for instance, by using radiation or chemical

substances, as it is clearly stated in recital 17 of Directive 2001/18/EC. With regard to the insufficient safety record of the new technologies, an application of Annex I B is not possible.

In addition, the described legal framework corresponds to the precautionary principle which characterizes the law on deliberate release in a way that is stated in the "Communication from the Commission of 2 February 2000 on the precautionary principle".

Only the application of Annex I A Part 1 to the new technologies guarantees the realization of the process approach which has a significant impact on the entire European law on genetic technology.

V. Zusammenfassung der wesentlichen Ergebnisse

Die mittels neuer Technologien erzeugten Organismen unterfallen dem Anwendungsbereich von Annex I A Teil 1 Nr. 1 der Richtlinie 2001/18/EG. Für dieses Ergebnis sprechen neben dem Wortlaut und der Historie der Bestimmung auch gesetzessystematische und teleologische Erwägungen.

Von besonderer Relevanz ist in diesem Zusammenhang der Umstand, dass sich Annex I A Teil 1 der Richtlinie 2001/18/EC - ausdrücklich anders als Annex I B - des Instrumentes einer nicht-abschließenden Auflistung bedient, um so die Anwendbarkeit des regulatorischen Rahmens gerade auch auf neue Technologien sicherzustellen.

Diese Erstreckung des Annexes I A Teil 1 Nr. 1 entspricht auch dem ausdrücklich erklärten Willen der Kommission, wie er vor allem in dem „Report on the Review of Directive 90/220/EEC in the Context of the Commission's Communication on Biotechnology and the White Paper“ erklärt worden ist.

Dass Mutationen als solche (sic!) natürlich durchaus vorkommen, spielt in diesem Zusammenhang keine Rolle. Ausschlaggebend für diese Feststellung ist der Umstand, dass das „nicht-natürliche Vorkommen“ nicht generell-abstrakt, sondern ausschließlich individuell-konkret zu beurteilen ist. Bei den mittels ODM oder vergleichbarer neuer Techniken bewirkten Veränderungen werden zielgerichtet in einem Organismus Veränderungen vorgenommen, die in dieser Weise in diesem konkret zur Beurteilung anstehenden Organismus mit Sicherheit nicht aufgetreten wären. Gerade weil es sich um zielgerichtete

Punktmutationen handelt, ist Annex I A Teil 1 Nr. 1 auf die sogenannten neuen Techniken anzuwenden.

Ergänzend gilt es bei der Beurteilung der in Frage stehenden Technologien zu berücksichtigen, dass die betreffenden Verfahren häufig hintereinander angewendet werden können - mit der Folge, dass es dann in der Summe zu längeren Veränderungen bis hin zum kompletten Genom-Austausch im Zielorganismus kommen kann.

Die mittels der neuen Technologien erzeugten Organismen unterfallen zusätzlich auch Annex I A Teil 1 Nr. 2 der Richtlinie 2001/18/EG. Hierfür spricht der Umstand einer nur beispielhaften („einschließlich“) Aufzählung bestimmter Technologien sowie die Tatsache, dass es ebenso möglich ist, Erbgut nicht nur direkt, sondern auch indirekt durch ein Vektor-System einzuführen.

Zusätzlich geht Annex I A Teil 1 Nr. 2 nicht von der konkreten Vererbung des betreffenden genetischen Materials, sondern lediglich von der Vererbungsfähigkeit, also dem grundsätzlichen Potential zur Vererbung aus. Schließlich gilt es in diesem Zusammenhang auch zu berücksichtigen, dass Annex I A Teil 1 Nr. 2 im Lichte der Intention des Europäischen Gesetzgebers zu interpretieren ist, der im Wege eines prozessorientierten Ansatzes schon den bloßen Einsatz gentechnischer Verfahren genügen lassen wollte, um den Anwendungsbereich der Richtlinie 2001/18/EG zu eröffnen.

Hingegen lassen sich die fraglichen neuen Verfahren eindeutig nicht dem Begriff der Mutagenese nach Annex I B der Richtlinie 2001/18/EC zuordnen. Für diese Bewertung spricht bereits das

Regel-Ausnahme-Verhältnis von Art. 2 der Richtlinie und Annex I A einerseits zu Art. 3 der Richtlinie und Annex I B andererseits.

Vor allem aber ist mit Nachdruck darauf hinzuweisen, dass der in Annex I B verwendete Begriff der Mutagenese ausdrücklich die konventionelle - also etwa mittels Bestrahlung oder über chemische Substanzen herbeigeführte - Mutagenese erfasst. Dies stellt bereits Begründungserwägung Nr. 17 zur Richtlinie 2001/18/EG ausdrücklich klar. Angesichts des vollkommen unzureichenden safety record für die genannten neuen Technologien ist es daher unmöglich, Annex I B auf die entsprechenden neuen Technologien anzuwenden.

Die vorstehend beschriebenen rechtlichen Rahmenbedingungen entsprechen zusätzlich auch dem das Freisetzungsrecht prägenden Vorsorgeprinzip in der Form, wie es durch die „Communication from the Commission of 2 February 2000 on the precautionary principle“ verbindlich ausgeführt worden ist.

Nur die Anwendung des Annex I A Teil 1 auf die neuen Technologien ist zudem geeignet, den verfahrensbasierten Regulierungsansatz zu verwirklichen, der das gesamte europäische Gentechnikrecht maßgeblich prägt.