New developments in modern biotechnology: 
A survey and analysis of the regulatory status of plants produced through 
New Breeding Techniques

Master thesis submitted in fulfillment of the degree of 
'Master in Law'

By

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Sam Odo Callebaut
Foreword and Acknowledgements

This thesis is written as the final part of a Master in Law programme at the University of Ghent, Belgium. It concludes an enriching, more than agreeable, and truly memorable chapter in my life.

First and foremost, I would like to thank my promotor, Prof. Mr. Drs. Pieter van der Meer, without whose kind assistance, expert advice and forthright remarks, I would have gotten lost in the complexity of the technical matter of genetic modification and modern biotechnology. More in particular, I would also like to thank him for inviting me to the eye-opening FDLI and CEPM seminars held at the end of 2014 in Brussels, Belgium, thus fueling my enthusiasm for the topic of biotechnology law.

A word of gratitude, also, for my copromotor, Dr. Merijn Chamon of the faculty of Law at the Ghent University, Dr. René Custers, regulatory affairs manager at the VIB, and Dir. u. Prof. Dr. Joachim Schiemann of the Julius Kühn Institute in Germany for reading my thesis and sharing their views with me.

I seize the opportunity to express my sincerest gratitude to my dear parents. Without their tremendous support and patience I would have never been able to complete this thesis.

Lastly, I would like to thank my sister Tina, my girlfriend Inés and my good friend Alberto for their moral support these last few months.

Ghent, 5 February 2015
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1. Introduction

1.1 New technologies and Law

Law often struggles to keep up with a rapidly advancing technological society. Discoveries, inventions and new techniques as a result of new developments in science often pose regulatory challenges to lawmakers:

Is the technological novelty - or its resulting products – covered by existing safety regulations, and - if not - should it be? If yes, is there need for a new regulatory framework, or, can the new technique be fit in an existing legal framework for a similar technique? How should a new framework be implemented?

Whereas lawmakers' responses to the above questions may vary, it is clear that it will almost always be a delayed response with regard to the development of the new technique. The technological novelty comes first, the regulatory actions come afterwards.

Only rarely a legislator can and will foresee future developments in science and adapt the current regulatory framework in order to address these future technological developments.

Not only lawmakers are burdened by said regulatory challenges. Legal subjects, such as research institutes -and companies, that wish to work with, and that are often the very origin of the new developments, face legal uncertainty:

Is the new technology and/or its products regulated, or in other words, does it fall within the scope of an existing legal framework? If not, will the new technique be regulated by a framework to come? If yes, how stringent will this future legal framework be? When will the new framework be implemented? What is allowed or prohibited in the meantime?

This uncertainty reflects on the conduct of these legal subjects involved. In attendance of a clear response to the above questions, and in fear of possible legal costs or repercussions, they will adopt a prudent approach in their activities. In turn, this prudent approach could entail a delaying effect on the further research and development of the new technique.

Therefore, these operators will need to find answers to these questions as soon as possible.
1.2 Modern biotechnology, genetic modification and GMOs

Modern biotechnology is a relatively young and rapidly developing field of science. The technique of genetic modification is a contemporary key tool.

Developed in the early 1970's, the process of genetic modification implies in essence the production of novel genetic combinations in an organism through the use of techniques that operate on the molecular level by either adding genes derived from a donor organism, or by altering or silencing the expression of an existing gene.

These introduced or altered traits vary greatly. From a faster growth of the plant or animal, through a higher yield, to resistance to a certain pest or disease, or tolerance to unfavourable environmental or weather conditions.

The transfer of genetic material derived from an organism that is not sexually compatible with the receiving organism is often referred to as "transgenesis". The transfer of genetic material derived from an organism that is sexually compatible with the receiving organism is often referred to as "cisgenesis".

Both these processes will hereafter be referred to as the "transfer/introduction of genetic material"; the distinction will be made whenever this is legally relevant.

In its conventional conception, the technical process of genetic modification involves in a first step the identification of a gene corresponding to a desirable trait in a donor organism, or a trait in the recipient organism, of which the expression is desired to be altered or silenced. The secession of the desired DNA in the donor organism is accomplished by a so-called restriction enzyme.

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1 Depending on the applicable regulatory context, different -but resembling- terms could have been used here: e.g. The Cartagena Protocol on Biosafety targets "Living Modified Organisms" (LMOs) and EU Regulation (EC) No 726/2004 targets -among others- “Recombinant DNA technology”.

As the main focal point of this thesis lies in the definition of "Genetically Modified Organism" in the EU regulatory system, the terms "GMO" and "genetic modification" are used here.


3 Which was in the 1970's still referred to as "Recombinant DNA techniques". In addition to recombinant DNA techniques, genetic modification can nowadays also be achieved by other techniques: cf. Infra.

4 It should be noted that the terms "transgenesis" and "cisgenesis" are not in any way mentioned in the EU regulatory system for GMOs. They are explained here because these techniques and the distinction between them are part of the current discussion with regard to the regulatory status of New Breeding Techniques.

For a more nuanced and in-depth outline of the technique of cisgenesis, refer to the corresponding subchapter 3.6.
Subsequently, this gene is adjusted so that it will function in the recipient organism and can next in various ways be transferred to the recipient organism, such as by means of insertion in a DNA-ring (plasmid) of an "Agrobacterium tumefaciens" bacterium. This technique of gene transfer through a new combination of DNA in a vector molecule outside of the organism's cell is referred to as "recombinant DNA".

In a final phase, the recipient organism is treated with the agrobacterium or vector system. The gene-carrying bacterium inserts the new gene (often called 'the gene of interest') into the recipient organism.

Together with the gene of interest, a selectable marker can be inserted as well, in order to be able to identify in which plant cells the gene transfer has been accomplished.

An alternative method of genetic modification of an organism is the vector-less direct introduction of the genetic material in said organism through mechanical means (e.g. "gene gun", or syringe)\(^5\). Direct vector-less introduction can also be accomplished through the use of electric currents or chemicals.

Another method of genetic modification of an organism is the 'induced' fusion of two or more cells.\(^6\)

Hereafter, these three base techniques will be referred to as "techniques of genetic modification".

1.3 GMOs and EU law

Recognizing the potential benefits of these new techniques for human well being and the environment, as well as the need to have in place systems to assess whether there are risks for human health and the environment, and the need to harmonise such systems, the European Union has been regulating the technique of genetic modification since the early 90's.

Following the international approach\(^7\), the first EC directives on the contained use of genetically modified micro-organisms (GMMs) (90/219/EC) and deliberate release in the environment of GMOs (90/220/EC) had been established in 1990.

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5 see: http://www.vib.be/nl/biotech-basics/Pages/DNA-knippen-en-plakken.aspx
6 The technique of genetic modification through cell fusion is in essence also a form of modification through direct introduction, as there is no vector system used. It is listed separately here because the EU GMO law makes this distinction as well.
7 Refer to: OECD Guidelines (1986) - Recombinant DNA: Safety Considerations (Blue Book)
Between 1998 and 2003, the EU framework on genetic modification and GMOs has undergone revisions as well as expansions: In 1998, the Directive for contained use was revised by Directive 98/81/EC. In 2001, Directive 90/220/EC was revised and replaced by Directive 2001/18/EC on the deliberate release of GMOs. In 2003, Regulations on GM food and feed, labelling and traceability of GMOs and on the transboundary movement have been established.

In a latest legislative step in 2009, a consolidating Directive on the contained use of Genetically Modified Micro-organisms has been adopted in replacement of Directive 90/219/EC.  8

In short, the EU regulatory framework for GMOs today comprehends five key legal documents:

- **Directive 2009/41/EC** of the European Parliament and of the Council of 6 May 2009 on the contained use of genetically modified micro-organisms (GMMs) 9 sets out rules for the contained use (e.g. laboratories, research greenhouses, process facilities) of GMMs. A risk assessment has to be carried out in order to determine the degree of risk involved in the contained use of the GMM. Based on this risk assessment, activities are divided into four classes. The Directive prescribes record keeping (class 1), notification (class 2) and authorisation (class 3 and 4) procedures for the contained use, as well as specific containment measures for each class.


- **Regulation (EC) No 1829/2003** of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed 11 prescribes an authorisation procedure for the placing on the market of food and feed products consisting of, containing, or produced from GMOs. The Regulation also stipulates that these products must be labeled as such.

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- **Regulation (EC) No 1946/2003** of the European Parliament and of the Council of 15 July 2003 on the transboundary movements of genetically modified organisms \(^{13}\) implements the Cartagena Protocol on Biosafety \(^{14}\) into the EU legal order. It sets out rules for the transboundary movement of GMOs from the EU to third countries. Different types of notification procedures have to be followed, depending on the nature of the product and on the nature of the movement.

In addition, the EU regulatory framework on GMOs includes:

- **Regulation (EC) No 65/2004** setting up a system for the assignment of Unique Identifiers for GMOs \(^{15}\),
- **Regulation (EC) No 882/2004** setting out rules for the official controls performed to ensure compliance with feed and food law \(^{18}\),
- **Decision 2004/204/EC** determining detailed arrangements for the registers recording information on GMOs \(^{19}\) and
- **Regulation (EU) No 503/2013** on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 \(^{20}\).

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These legislative documents are supplemented with a number of guidance documents in the form of Commission and Council Decisions and Recommendations, such as:

- **Decision 2002/623/EC** establishing guidance notes supplementing Annex II to Directive 2001/18/EC 21,
- **Decision 2002/811/EC** establishing guidance notes supplementing Annex VII to Directive 2001/18/EC 22,
- **Recommendation 2004/787/EC** on technical guidance for sampling and detection of GMOs 23,
- **Recommendation 2010/01/EC** on guidelines for the development of national coexistence measures to avoid the unintended presence of GMOs in conventional and organic crops 24 and
- **Decision 2009/770/EC** establishing standard reporting formats for presenting the monitoring results of the deliberate release into the environment of GMOs, as or in products, for the purpose of placing on the market, pursuant to Directive 2001/18/EC 25.

The main objectives of this EU regulatory framework can be summarized as a combination of 1) the protection of human and animal health and the environment 26, 2) the improvement of the free movement of GMOs and internal market in the EU through the approximation of the laws, regulations and administrative provisions of the Member States 27 and 3) the protection of a free and informed consumer’s choice with regard to GM food. 28

In its regulatory approach for genetic modification and GMOs, the EU envisages an extensive harmonisation of the regulatory systems of the member states.

Directive 2009/41/EC on the contained use of GMMs finds its legal basis in article 192 of the Treaty on the Functioning of the European Union (ex-article 175 TEC), which corresponds to the objective of the protection of human and animal health and the environment. It therefore sets out minimum standards: the transposition by the member states may establish rules that are stricter, but not less

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26 cf. Recital 4 and 5 of Directive 2001/18/EC
27 cf. Article 1 of Directive 2001/18/EC
strict than the rules set out in this environmental directive.  

Directive 2001/18/EC on the deliberate release of GMOs on the other hand, finds its legal basis in article 114 of the TFEU (ex-article 95 TEC), which corresponds to the objective of the establishment and functioning of the internal market. It therefore sets a standard for the member states and leaves little room for appreciation: the transposition by the member states must be in accordance with this internal market directive.

Whereas the above-listed EU Regulations have different legal bases and therefore different objectives, they do not require transposition by the member states and are directly applicable in the national legal orders.

In addition to the abovementioned framework specifically targeting genetic modification and GMOs, the EU also indirectly regulates genetic modification and GMOs by means of a large number of laws targeting related and/or from genetic modification potentially derived practices, products and rights.

With regard to public information and participation in EU legislative and administrative decisions concerning GMOs, Regulation (EC) No 1049/2001 guarantees a general – but limited and conditional - right of access to all documents drawn up or received by the European institutions in all areas of activity of the EU.

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29 e.g. Member states could in diversion of Directive 2009/41/EC establish rules that prescribe authorisation procedures for class 1 and 2 GMMS as well. The scope could be extended to include GMO plants and animals. Among others Belgium (Flemish region) and The Netherlands have made use of this freedom in the transposition.

30 The imperative harmonising nature of Directive 2001/18/EC is however mitigated by article 23 of said Directive: the so-called "safeguard clause" allows individual member states to provisionally restrict or prohibit the use and/or sale of GMOs on their territory when new or additional information affecting the environmental risk assessment or the reassessment of existing information on the basis of new or additional scientific knowledge, has detailed grounds for considering that a GMO as or in a product which has been properly notified and has received written consent under this directive constitutes a risk to human health or the environment.

Article 23 is consistent with article 114 TFEU, as the latter in (5.) explicitly provides an opt-out possibility for a member state if that state “...deems it necessary to introduce national provisions based on new scientific evidence relating to the protection of the environment or the working environment on grounds of a problem specific to that Member State arising after the adoption of the harmonisation measure...”

The new Directive (EU) 2015/412 amends Directive 2001/18/EC and further mitigates the harmonising nature of the EU regulatory system for GMOs. It inserts article 26 b, which grants member states the possibility to decide during or after the authorisation procedure whether or not they want to allow the cultivation of GMOs on their territory. These ‘opt-out’ measures may be based on grounds related to, among others, environmental policy objectives, land use, socio-economic impacts, and agricultural policy objectives.


31 e.g. Regulation (EC) No 1829/2003 finds its legal base in articles 43, 114 and 168 (4b) TFEU; Regulation (EC) No 1830/2003 finds its legal base in article 114 TFEU; Regulation (EC) No 1946/2003 finds its legal base in article 192 TFEU.

32 The subsequent list of regulatory documents is by no means intended to be exhaustive. Only the for this thesis most relevant documents are listed. For a more extensive and detailed overview, refer to: Users Guide to European Regulation in Biotechnology, European Commission, Contract no. FIF.2004 0828
Implementing the Aarhus Convention \(^{33}\) and \textbf{Directive 2003/4/EC} and \textbf{Directive 2003/35/EC} respectively warrant public access to information and public participation in all environmental matters.

Directive 2001/18/EC\(^{34}\) and Regulation (EC) No 1829/2003\(^{35}\) also contain specific provisions with regard to public information during authorisation procedures under these laws.

Medicinal use of genetic modification and GMOs is highly regulated in the EU. A plethora\(^{36}\) of regulatory documents cover biotechnology derived medicinal products\(^{37}\) for human and veterinary use.


In the EU, intellectual property rights with regard to biotechnological inventions for agricultural and industrial use is respectively protected by plant variety and patent rights.

Plant variety rights with regard to GMOs are covered by \textbf{Directive 2002/53/EC} and \textbf{Directive 2002/55/EC}, which establish the general framework for plant and vegetable variety rights in the EU. There (currently) is no EU patent system as such in place.\(^{38}\)


\(^{34}\) Articles 9, 24, 25

\(^{35}\) Articles 29, 30

\(^{36}\) Only the for this thesis most relevant documents are listed here.

\(^{37}\) Regulation (EC) No 726/2004 covers "\textit{Medicinal products developed by means of one of the following biotechnological processes: - recombinant DNA technology - controlled expression of genes coding for biologically active proteins in prokaryotes and eukaryotes including transformed mammalian cells, - hybridoma and monoclonal antibody methods}" (Article 3.1 j° ANNEX). While these scope terms remain undefined in the law, it is clear that there is a certain similarity and overlap in meaning with the legally defined term "GMO".

\(^{38}\) Patents in Europe are either granted under the national system of the European states or under the system run by the European Patent Organisation (EPO). The patent granted under the EPO system only has effect in the designated countries. The patent system run by the EPO under the European Patent Convention (EPC) has strictly speaking no ties to the EU regulatory system. This is an international, rather than a supranational or community system. It counts multiple
There is however one EU legislative document specifically targeting the patentability - and the harmonisation thereof - of biotechnological inventions: Directive 98/44/EC both determines and limits the patentability of these inventions.

Environmental liability with regard to the transport, use and release of GMOs is covered by Directive 2004/35/EC. The ‘Environmental Liability Directive’ covers damage to protected species, natural habitats, water and soil. It sets up a specific liability regime for operators who professionally conduct risky or potentially risky activities. The Directive qualifies the transport, use and release of GMOs as such activities.

1.4 New developments in modern biotechnology

Since the first applications in the 1970's, the 'conventional' process of genetic modification has been subject to numerous scientific developments. These developments have resulted in tweaks, changes and variations to the modification method.

With increasing knowledge of genetics and molecular biology, researchers have started to build on and divert from the conventional genetic modification method in an attempt to streamline and improve the breeding process in general.

In other cases, sheer experimental coincidence and research into observed phenomena have led to the development of new techniques and variations of existing techniques.

As a result of these developments, a number of new breeding techniques have emerged. These techniques are often referred to as "New (Plant) Breeding Techniques", or NBTs. Examples of these techniques include: Oligonucleotide Directed Mutagenesis (ODM), Zinc Finger Nuclease

contracting parties who are not EU member states. However, Regulation (EU) No 1257/2012 and Regulation (EU) No 1260/2012 will make it possible to obtain a "European patent with unitary effect" under the EPO system. These regulations are applicable as soon as the Agreement on a Unified Patent Court is ratified by at least 13 member states. So far, only five out of twenty-five contracting states have ratified this agreement.

39 This term is to a large extent a misnomer. The techniques are not necessarily "new", as some of these techniques (e.g. cisgenesis) have already been applied since the early days of genetic modification; other techniques (e.g. grafting (on GM rootstock)) merely involve the combination of two or more conventional techniques.

They are not necessarily used to process "plants": they may also be used to process animals or micro-organisms. They are not necessarily used for "breeding": some techniques (e.g. agro-infiltration) are to a large extent used for laboratory testing.
Technology (ZFN), cisgenesis, grafting on GM rootstock, agro-infiltration, RNA-dependent DNA methylation (RdDm), reverse breeding and Synthetic Genomics.\textsuperscript{40}

These new techniques – in general - allow a faster, more specific and/or more efficient breeding process than the 'conventional' modern biotechnological methods.\textsuperscript{41}

Some of the New Breeding Techniques involve the use of a technique of genetic modification in an intermediate step, but without an actual transfer or incorporation of genetic material taking place: e.g. a genetic alteration could be accomplished by an induced targeted mutation of the native genetic material in the plant.\textsuperscript{42}

Examples of these techniques making use of this process are "site-directed mutagenesis" or "targeted mutagenesis".\textsuperscript{43}

Other new techniques do not necessarily entail a lasting genetic alteration and expression in a targeted organism, but only result in temporary – transient - effects in this organism. Or, in other cases, a genetic modification is merely used in an intermediate step of the breeding process of an ultimate elite plant, but the genetic change cannot be distinguished from conventionally bred results.

This heterogeneous ensemble \textsuperscript{44} of techniques are the so-called "Negative segregants" \textsuperscript{45} or "Transgenic construct-driven breeding techniques"\textsuperscript{46}.

A last number of techniques make use of the conventional genetic modification method (gene introduction through an agrobacterium or other vector system, vector-less direct introduction or cell fusion), but the resulting organism they finally generate, raises questions with regard to its legal qualification: The resulting organism is a mixture of non-GM tissue and GM tissue\textsuperscript{47}, or only carries

\textsuperscript{40} These techniques and their regulatory status will hereunder be outlined and discussed in chapter 3.
\textsuperscript{42} This kind of genetic alteration is also referred to as "Genome editing". 
\textsuperscript{cf.} oral presentation Prof. Mr. Drs. Pieter van der Meer, CEPM conference, "Revision of the GMO Directive: Reconciling a globalised market with national GMO regulations in the EU. What solutions to ensure the competitiveness and coexistence of sectors?", 9 December 2014, Brussels.
\textsuperscript{43} See: ODM, ZFN-1 and ZFN-2. Other techniques of “Genome editing”; but not examined in this thesis are, among others, TALEN, CRISPR and Meganuclease techniques.
\textsuperscript{44} The techniques studied in this thesis are: reverse breeding, RdDm and agro-infiltration.
\textsuperscript{45} PARISI, C., 2012 \textit{New plant breeding techniques: State-of-the-art, potential and challenges}; doctoral thesis biosciences and agri-food sciences University of Córdoba, Spain
\textsuperscript{46} LUSSER et al. 2011
\textsuperscript{47} Grafting of a non GM scion on a GM rootstock or vice versa.
sequences derived from a sexually compatible species.\textsuperscript{48}

1.5 NBTs and EU law

These particular technical characteristics raise questions with regard to the regulatory status of organisms produced through these New Breeding Techniques: Are the organisms resulting from the application of these NBTs legally considered "GMOs"? And if so, are these organisms captured by the scope of the existing regulatory framework for contained use, experimental release, placing on the market, transboundary movement, traceability and labelling of GMOs?

Even though the relatively young European Union legislation with regard to GMOs has undergone multiple expansions, amendments and revisions since its establishment in 1990, it should be stressed that the definition of the key scope term "GMO" in itself was never really substantially adapted\textsuperscript{49} and still largely corresponds to the definition originally established in Directive 90/220/EC.\textsuperscript{50}

Given that the wording of the 1990 legal definition was inspired by the way modern biotechnology and genetic modification were put in practice in and before 1990, it was undoubtedly fit to apply to modern biotechnological practices and genetic modification back then. However, almost 25 years later, the question arises whether the definition adequately addresses organisms produced through these new breeding techniques of modern biotechnology.

As these questions have not yet been explicitly answered by the European Commission or by the EU legislator\textsuperscript{51}, scientists and other operators involved in the research and development of NBTs today

\begin{flushright}
\textsuperscript{48} Cisgenesis
\textsuperscript{49} Nevertheless, the text of the current GMO definition is not entirely the same as the text of the definition established in Directive 90/220/EC. For an overview of the differences between the definitions in the 2001/18/EC and 90/220/EC directives, refer to chapter 2.1 "The GMO regulatory framework in the EU".
\textsuperscript{50} Despite the Commission's intention to regularly update Directive 90/220/EEC in function of scientific and technological progress, see: COM(88)6397, p. 34; COM(96)630final, p. 10
\textsuperscript{51} The new President of the EU Commission has, in advance of the European Parliament's vote on 15 July 2014 however announced a review of the legislation applicable to the authorisation of GMOs. It is still unclear if this review will affect the definition of "GMO" in the EU regulatory system. Refer to http://www.europarl.europa.eu/EPRS/EPRS-Briefing-538963-Setting-EU-Priorities-2014-19-FINAL.pdf
\end{flushright}
face uncertainty with regard to the legalities linked to their activities.\textsuperscript{52}

In recent years, a number of scientific experts, expert groups and advisory committees\textsuperscript{53} have discussed the legal questions at hand. Based on arguments derived from gathered scientific knowledge and experience with the techniques, these experts have formulated an assessment with regard to the regulatory status.\textsuperscript{54}

In addition to the technical assessment, these expert reports have repeatedly underlined the need for more legal clarity with regard to the regulatory status of the organisms produced through New Breeding Techniques.

1.6 Research question and outline of the thesis

This thesis conducts a survey with regard to the regulatory status of plants produced through New Breeding Techniques and attempts to assist the formulation of an answer to the most pressing legal questions at hand.

More specifically, the thesis examines the organisms produced through these techniques in the light of the current legal notion of "GMO" in the EU.

The thesis focusses on New Breeding Techniques in practice (i.e. research and/or development) used in European laboratories today.

In 2008, the European Commission charged an expert group called the "New Techniques Working

\textsuperscript{52} In this context it should be noted that authorisation procedures for the commericalisation of GMOs in Europe entail an immense legal cost, sometimes ranging in the tens of millions of euros. Procedures may take up multiple years.


\textsuperscript{54}For a recent and noteworthy survey prepared by private stakeholders, refer to: Legal Briefing paper – The regulatory status of plants resulting from New Breeding Techniques, produced by the NBT Platform, April 2014 (not public)
Group” (NTWG) with the task to establish a list of the most relevant and actual new breeding techniques and to evaluate the regulatory status of organisms produced through the techniques listed.\(^{55}\)

In 2012, the NTWG issued its conclusions in a final report, in which it was evaluated whether and to what extent the organisms obtained through the techniques listed were covered by the GMO definition, based on mostly scientific, technical and other arguments.\(^{56}\)

This thesis has partly the same objective with the notable difference that it will only focus on legal arguments in a profound and broad sense.

The list of the most relevant techniques as established in 2008 by the NTWG and also cited and described by, among others, Lusser, M., 2011\(^{57}\) is still largely up to date. Therefore the techniques listed by the NTWG in 2012 will be the techniques considered in this thesis.\(^{58}\)

The following techniques will be evaluated:

- Oligonucleotide Directed Mutagenesis (ODM),
- Zinc Finger Nuclease Technology (ZFN)\(^{59}\),
- cisgenesis, grafting on GM rootstock,
- agro-infiltration,
- RNA-dependent DNA methylation (RdDm),
- reverse breeding.

The thesis maintains a focus on the regulation of plant breeding.

While it is recognised by the NTWG as a New Breeding Technique, the ensemble of new and emerging techniques referred to as "Synthetic Genomics"\(^{60}\), and their versatile (potential) applications, broadly exceed the field of plant breeding. For that reason, the regulatory status of organisms


\(^{56}\) It should be noted that the conclusions in the NTWG report do not necessarily represent the official opinion of the EU authorities on the legal status of NBPs. The EU is still assessing the safety aspects of these techniques through the European Food Safety Authority: so far, EFSA has formulated opinions on cisgenesis, intragenesis and Zinc Finger Nuclease 3. It is not (yet) clear if, and when the EU will formulate an official opinion on the regulatory status of NBPs.

\(^{57}\) LUSser et al. 2011, cf. supra

\(^{58}\) In addition, this list of techniques has also been cited by the OECD Working Group on Harmonisation of Regulatory Oversight in Biotechnology as the reference list of NBPs. Refer to the summary of the responses to a questionnaire that circulated prior to the Working Group's Workshop on Environmental Risk Assessment of New Plant Breeding Techniques in February 2014.

\(^{59}\) Zinc Finger Nuclease Technology (ZFN) is a form of Site Directed Nuclease Technology (SDN). For the sake of uniformity with the NTWG and JRC report, this thesis will only focus on the regulatory status of the plants produced through ZFN. The subsequent legal assessment with regard to the plants produced through ZFN \textit{mutatis mutandis} applies to plants produced through other forms of SDN, such as TALEN, CRISPR and Meganucleases: these techniques all work according to the same general principles.

\(^{60}\) “Synthetic Biology is the engineering of biological components and systems that do not exist in nature and the re-engineering of existing biological elements; it is determined on the intentional design of artificial biological systems, rather than on the understanding of natural biology.”, Synbiology – An analysis of synthetic biology research in Europe and North America
produced through these techniques will not be discussed in this thesis.

This thesis examines the topic of NBTs in the regulatory framework of the EU in this area. A study limited to a national regulatory framework of one of the EU member states, which is in essence the mere local expression of a broader international policy, would be less relevant and useful.

**1.7 Approach**

In the first chapter, named "The GMO and its legal reflection in the EU", the thesis provides an overview of the current definition of a GMO in the European Union. Based on a number of highlighted ambiguities arising from the practical application of the European legal definition of "GMO" on organisms produced through NBTs, the thesis will reflect on legal interpretative clues in an effort to outline the extent of the scope of this definition. Legislative documents, legal guidelines and other interpretative documents, as well as relevant jurisprudence and doctrine in this area will be examined.

The subsequent chapter, named "The EU regulatory status of plants produced through NBTs", analyses whether, and – if so - to what extent the resulting organisms of the New Breeding Techniques are captured by the scope of the current legal definition of "GMO" and the regulatory framework for GMOs. Technique by technique will be evaluated in the light of the conclusions in the preceding chapter.
2. The GMO and its legal reflection in the EU

In order to get a clear idea of the scope of the EU legal notion of "GMO", the actual legal framework regulating GMOs sensu stricto has to be distinguished from other legal instruments targeting related and/or from genetic modification potentially derived practices, products and rights.61

2.1 The GMO regulatory framework in the EU

"GMO" according to the law

"GMO" is the key scope term in EU biotechnology law sensu stricto. Directive 2001/18/EC on the deliberate release of GMOs provides a definition that serves as the reference definition for the ensemble62 of GMO legislation in the EU.

Article 2(2) of Directive 2001/18/EC defines a GMO as follows:

'An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally through mating and/or natural recombination'. 63

In addition, article 2(2)(a) of the Directive refers to a list of techniques in Annex IA Part 164 that are explicitly included within the terms of the definition:

61 These instruments do not necessarily use the scope term "GMO". Instead, a different but resembling term is sometimes used. e.g. Directive 98/44/EC targets -among others- "a product consisting of or containing biological material or a process by means of which biological material is produced, processed or used." Regulation (EC) No 726/2004 targets -among others- "Recombinant DNA technology". These legal terms and their application on plants and organisms produced through NBTs will not be discussed in this thesis.

62 With the exception of Directive 2009/41 on the contained use of Genetically Modified Micro-organisms which targets GMMs instead. The legal definitions for a GMM and a GMO are however largely the same, with two notable differences: (1) the term "GMM" obviously considers micro-organisms instead of organisms, and (2) micro-organisms produced by self-cloning are explicitly excluded from the 2009/41 scope. Self-cloned organisms are not excluded from the 2001/18 scope. See: Annex II part A, 4. of the Directive.

63 With "An organism" being defined as: 'any biological entity capable of replication or of transferring genetic material' (Article 2(1))

64 Annex I A Part A in Directive 2009/41/EC
'Within the terms of this definition:

(a) genetic modification occurs at least through the use of the techniques listed in Annex IA, part 1;

Annex IA Part 1 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 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 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.'

Article 2(2)(b) refers to a list of techniques in Annex IA Part 2 that are explicitly excluded from the definition of genetic modification:

'(b) the techniques listed in Annex IA, part 2, are not considered to result in genetic modification;

Annex IA Part 2 reads:

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

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

(3) polyploidy induction.’

Lastly, article 3(1) exempts\textsuperscript{65} a number of techniques of genetic modification from the Directive's scope by referring to annex IB:

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

Annex IB reads:

‘Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they 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.’

In short, and in a \textit{prima facie} literal interpretation, the above implies that an organism in which the genetic material has been altered in a way that does not occur naturally through mating and/or natural recombination, is a GMO. (\textbf{General prescription})

In particular, an organism in which the genetic material has been altered through, \textit{inter alia}, the use

\textsuperscript{65} It is relevant to note the difference between the \textit{exclusion} from the definition and the \textit{exemption} from the scope of the directive. The organisms obtained through the use of techniques that are excluded from the definition are not to be considered GMOs, and therefore, the GMO legislation is not applicable to these organisms. Whereas the organisms obtained through the use of the techniques that are exempted from the directive may meet the GMO definition, they could still be captured by other GMO legislation that does not exempt these organisms.
of a recombinant DNA technique, vector-less direct introduction, or cell fusion is a GMO. (Including prescription)

An organism in which the genetic material has been altered through the use of in vitro fertilisation, natural processes such as conjugation, transduction and transformation or polyploidy induction is not a GMO, unless these techniques or processes involved the use of recombinant nucleic acid molecules or GMOs. (Excluding prescription, with exception)

An organism in which the genetic material has been altered through the use of mutagenesis or cell fusion is exempted from GMO legislation, unless these techniques or processes involved the use of recombinant nucleic acid molecules or GMOs. (Exempting prescription, with exception)

As mentioned before, this definition still largely corresponds to the GMO definition as originally set out by Directive 90/220/EC. There are however a number of apparent differences:

- Directive 2001/18/EC added "..., with the exception of human beings...," to article 2(2). 66


Since Council Recommendation 82/472/EEC67 defines "Work involving recombinant DNA" as: "the formation of new combinations of genetic material by the insertion of nucleic acid molecules produced by whatever means outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation.", it is clear that this corresponds to the current content of indent (1) of Annex IA Part 1 of Directive 2001/18/EC.

- Directive 2001/18/EC has expanded Annex IA Part 2 and Annex IB respectively with: “on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms made by techniques/methods other than those excluded by Annex IB” and

67 Council Recommendation 82/472/EEC concerning Notification of Work involving recombinant Deoxyribonucleic Acid (DNA) is the first EU legal document addressing genetic modification – back then still referred to as “Recombinant DNA”.

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“other than those produced by one or more of the techniques/methods listed below...”.

To sum up, this very limited list of 'changes' supports the premise that the current GMO definition in Directive 2001/18/EC still largely corresponds to the one set out in Directive 90/220/EC. It is safe to conclude that the text of the EU GMO definition has not been substantially changed since its initial redaction.

With regard to the cited parts of Annex I, it should be noted that the techniques listed in Annex IA Part 1 correspond to the three classic techniques of 'conventional' genetic modification: genetic modification through recombinant DNA (bacterium, virus or other vector system), through vector-less direct introduction of DNA and through cell fusion.

The techniques listed in Annex IA Part 2 and Annex IB represent techniques and processes of genetic modification that have conventionally been used in a number of applications and have -according to the lawmaker- a long safety record\(^{68}\), and/or could occur spontaneously in natural conditions.

2.1.1 Key interpretative issues when applied organisms obtained through NBTs

Despite the definition's general and broad\(^{69}\) character, and despite its structured and seemingly clear redaction, a number of questions have arisen when applying it to New (Plant) Breeding Techniques and the organisms obtained through the use of these techniques.

Precisely because of its general and broad character, certain terms of the definition could appear to be open for interpretation.

Depending on the interpretation used for a particular term, some of the techniques discussed would in some cases give rise to a GMO, and in other cases not. In addition, while some of the techniques discussed may give rise to a GMO, it is not clear if this organism is captured by the provisions of the GMO legislation.

Hereafter, these terms and issues will be discussed individually, whereby the possible interpretations will be addressed.

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\(^{68}\) See: Recital 17 of Directive 2001/18/EC
\(^{69}\) Or "vague" from an operator's s point of view?
A. "...altered in a way..."

'An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally through mating and/or natural recombination'.

These key terms in the general prescription of the definition (article 2 (2) of Directive 2001/18/EC) are not entirely clear or conclusive.

In 1990, the practical application of a conventional technique of genetic modification typically entailed the incorporation of a new combination of genetic material in the modified organism: i.e. a new combination of DNA was added to the genetic material of the plant. Today, this is no longer necessarily the case. As mentioned before, several New Plant Breeding Techniques are based on a purely auxiliary use of the conventional techniques of genetic modification, but do not necessarily establish an organism in which the genetic material contains new combinations of genetic material. A DNA transfer is sometimes a mere step in the entire modification process.

"...altered in a way..." can be interpreted in three ways:

- "...altered in a way..." only refers to the techniques and processes used. The mere use of one of the conventional modification techniques, suffices for a resulting organism to be captured by the legal definition of a GMO. Whether or not this establishes (a) new combination(s) of genetic material in the resulting plant, is not relevant. In this interpretation, "genetically modified" organisms that are indistinguishable from organisms that could also be obtained through natural processes, natural breeding or the techniques listed in Annex IA Part 2 and Annex IB, would also fall under the definition. This is the so-called ‘process- or technique-based’ interpretation.

- "...altered in a way..." only refers to the resulting organism itself. The alteration is expressed

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70 Article 2 in Directive 2009/41/EC
71 And other techniques? Refer to subchapter 2.1.12 on "inter alia" and similarity.
by the establishment of (a) new combination(s) of genetic material \(^{72}\) in the resulting organism's genome, regardless of the technique used. Only if the resulting organism does in fact contain a new combination of genetic material “...that does not occur naturally...”, it is captured by the legal definition.

This is the so-called ‘product-based’ interpretation.\(^{73}\)

- "...altered in a way..." refers to both the techniques/processes and the resulting organism itself. A GMO is only legally established when a genetic modification technique is used, and this gives rise to an organism that contains (a) new combination(s) of genetic material “...that does not occur naturally...”.

This corresponds to a combination of the above two interpretations.

In addition, the question arises what an “alteration that does not occur naturally” exactly is. How much change is required to legally consider it an “alteration that does not occur naturally”? \(^{74}\)

In natural conditions and during traditional breeding, plants are susceptible to frequent changes and variations in their genome. As the law does not establish an exact technical threshold with regard to which changes should be considered “natural”, the question arises where the line should be drawn.

This question is relevant in the context of: ODM, ZFN, reverse breeding, RNA-dependent DNA methylation (RdDm), agro-infiltration and cisgenesis.

While reverse breeding, RdDm and agro-infiltration involve the use of a technique of genetic modification, they do not necessarily \(^{75}\) establish an organism that contains (a) new combination(s) of genetic material. For that reason, it is not clear if the resulting organisms are captured by the GMO definition.

\(^{72}\) Indent (1) and (3) of Annex IA Part 1 respectively refer to “new combinations of genetic material” and “new combinations of heritable genetic material” in the organism.

\(^{73}\) A well-known example of a product-based GMO definition and regulation can be found in the Canadian regulatory system for GMOs. The Canadian Food Inspection Agency (CFIA) defines a GMO as follows: “An organism, such as a plant, animal or bacterium, is considered genetically modified if its genetic material has been altered through any method, including conventional breeding.”

It will hereafter be evaluated if the same interpretation can be given to the GMO definition in the EU regulatory framework.

\(^{74}\) This question is only relevant if the GMO definition does in fact contain an emphasis on the result obtained through the application of GM techniques.

\(^{75}\) RdDm does in some cases establish an organism that contains (a) new combination(s) of genetic material: cf. Infra.
The regulatory status of the plants obtained through ODM, ZFN and cisgenesis is linked to the terms “...altered in a way...” in relation with the prescription “...that does not occur naturally through mating and/or natural recombination.”

Under the process- or technique-based interpretation, it appears that this condition is solely tied to the process/technique used to obtain an organism. As ODM, ZFN and cisgenesis involve the use of a GM technique (“...that does not occur naturally...”), the plants obtained through these techniques would be captured by the GMO legislation.

Under the product-based interpretation, the plants obtained through ODM, ZFN and cisgenesis would not be captured by the GMO legislation: the new combination(s) obtained through ODM, ZFN and cisgenesis do occur naturally.

Under the combined interpretation, it appears that this condition is both tied to the process/technique used to obtain an organism and the new combination of genetic material. Whereas ODM, ZFN and cisgenesis involve the use of a GM technique (“...that does not occur naturally...”), they do not result in the formation of a new combination of genetic material (“...that does not occur naturally...”): the plants obtained through ODM, ZFN and cisgenesis would therefore not be captured by the GMO definition.

B. "Heritable material"

‘(2) techniques involving the direct introduction into an organism of heritable material prepared outside the organism including micro-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.’

The terms "heritable material" and "heritable genetic material" are used in Annex IA Part 1, (2) and
At the time of the redaction of the definition, genetic modification was typically aimed at the inheritance and propagation of DNA or RNA in the recipient or host organism.

Some of the modern techniques making use of a direct introduction of genetic material however, involve a purely auxiliary use of genetic material, without an actual inheritance of this material into the targeted organism's genome taking place. Genetic material could be introduced in a host organism with the sole function of serving as a template with regard to a gene repair in the host organism by native repair enzymes.\(^77\)

While the introduced genetic material will not be inherited in the organism's genome, the induced genetic changes in the organism will however be inherited, propagated and passed on to offspring.

As the wording in Annex IA Part 1 (2) speaks of the "direct introduction" of the heritable material, the question arises whether or not this means that the introduced DNA or RNA should actually be inherited in the organism for a technique to be considered a “technique of genetic modification” within the terms of the GMO definition.

"Heritable material" could be interpreted in two ways:

- The introduced material must actually be inherited by the targeted organism.

- It is possible that this introduced material could be inherited: the introduced genetic material must simply be able to be inherited in the genome of the organism, in order for a technique to be considered a "technique of genetic modification".

Techniques for which this issue is relevant to the regulatory status of the resulting organisms are: Oligonucleotide Directed Mutagenesis (ODM) and Zinc Finger Nuclease (ZFN). While these techniques involve the direct introduction of genetic material in an organism, this genetic material is not necessarily\(^78\) incorporated in the organism's genome and passed on to offspring.

\(^76\) Annex I Part A (2) and (3) in Directive 2009/41/EC
\(^77\) e.g. ODM and ZFN-2
\(^78\) ZFN does in some cases (i.e. ZFN-3) introduce genetic material that is incorporated in the organism's genome: cf. Infra.
C. Is a GMO offspring a GMO?

A number of new breeding techniques comprehend a multi-step breeding process, in which a genetic modification is only used as an intermediate step. In subsequent steps in the process, the modified 'intermediate' organisms are induced to reproduce, where after the resulting offspring organisms do not necessarily contain a genetic alteration.

As the current legal definition does not explicitly address this issue, the question arises whether, and to what extent the offspring of a GMO would be captured by the definition.

In this context, it should be noted that reproduction in plants is not necessarily sexual.

- Sexual reproduction entails an offspring that is the product of two parent organisms.

- Vegetative reproduction entails an offspring that is the product of one parent organism. The offspring is a clone of its parent.

Techniques for which this issue is relevant to the regulatory status of the resulting organisms are the transgenic construct-driven breeding techniques reverse breeding and RNA-dependent DNA methylation (RdDm). These techniques involve in an intermediate step the reproduction of a genetically modified organism, where after the offspring organism(s) does/do not necessarily contain an alteration of the genetic material.

D. Transient presence and expression

The use of some of the transgenic construct-driven breeding techniques does not entail a lasting presence of introduced genetic material in an organism. Instead, the organism only temporarily contains this genetic material. This may lead to transient effects in the phenotype.

In some cases, the presence and/or effects caused by introduced genetic material in the organism last
a few hours. In other cases, the presence and expression of this genetic material is passed on to one or more next generation(s), but will eventually be extinguished.

As the current legal definition does not explicitly address this issue, the question arises to what extent an organism that only temporarily contained inserted genetic material, is a GMO.

Techniques for which this issue is relevant to the regulatory status of the resulting organisms are agro-infiltration, Zinc Finger Nuclease (ZFN) and RNA-dependent DNA methylation (RdDm). In some cases of agro-infiltration, new genetic material is introduced in an organism, and leads to a temporary and transient change in the expression level of a part of the recipient's native genetic material. The introduced genetic material is not incorporated in the recipient's genome and hereafter disappears. In the case of ZFN and RdDm, genetic material is introduced in an organism to respectively induce (a) mutation(s) in the genome and changes in the methylation of the recipient's DNA. The used genetic material disappears over time.

E. “Recombinant nucleic acid molecules”

'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: ...

'Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they 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: ...

The term "recombinant nucleic acid molecules" is mentioned in Annex IA Part 2 and Annex IB of Directive 2001/18/EC. The techniques listed in these parts of Annex I are respectively excluded from

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79 Agro-infiltration may also involve the use of Recombinant techniques; in those cases, the technique will result in a stable, and not transient alteration. Generally, the alteration will only be present in a part of the plant, (e.g. leaves).

the GMO definition and exempted from the Directive, unless they involve the use of "recombinant nucleic acid molecules".

As this term is not defined in the directive, the question arises what constitutes a “recombinant nucleic acid molecule”.

Whereas there is no doubt that it implies the formation of a new combination of genetic material outside of an organism’s cell \(^{81}\), the question is what exactly constitutes a new combination. Does the replacement of just one nucleotide in a sequence entail a new combination in the sense of the law? Or does it take more than that?

Techniques for which this issue is relevant to the regulatory status of the resulting organisms are Oligonucleotide Directed Mutagenesis (ODM) and Zinc Finger Nuclease (ZFN). These techniques both involve the introduction of synthesized DNA sequences\(^ {82} \) \(^ {83} \) in an organism, entailing a genetic change through a mutation in the organism.\(^ {84} \)

While it is clear that these techniques are similar (\textit{cf. infra: “...inter alia...” and similarity}) to the from the Directive exempted technique of “mutagenesis”, the question is whether these techniques are captured by the exception to the exemption “on the condition that they do not involve the use of recombinant nucleic acid molecules...” in Annex IB of Directive 2001/18/EC.

\textbf{F. “...inter alia...” and similarity}

\textit{‘Techniques of genetic modification referred to in Article 2(2)(a) are \textit{inter alia}: ...’}

Annex IA Part 1 of Directive 2001/18/EC uses the wording “inter alia”, and therefore the list of techniques in said annex appears to be of an indicative nature.

\(^{81}\) (1) of Annex IA Part 1 refers to “recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the introduction 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”\(^ {82} \)
\(^{83} \) With the exception of ZFN-1.
\(^{84} \) There is little to no debate whether or not these sequences should be considered "nucleic acid" in the sense of the law: this is DNA.
\(^{84} \) In the case of ZFN-3, the genetic change is obtained through the introduction of genetic material.
The question is to what extent other molecular modification techniques are also captured by Annex IA Part 1.

In addition, with regard to the techniques listed in Annex IA Part 2 and Annex IB of Directive 2001/18/EC, which are respectively excluded from the GMO definition and exempted from the Directive, the question is to what extent these provisions capture techniques similar to the ones explicitly listed.

The regulatory status of organisms produced through RNA-dependent DNA methylation (RdDm), Oligonucleotide Directed Mutagenesis (ODM) and Zinc Finger Nuclease (ZFN) is to subject to the response to this question.

The application of these techniques establishes organisms that are similar to the organisms obtained through the use of the techniques enumerated in Annex IA Part 1, Annex IA Part 2 and Annex IB of Directive 2001/18/EC, but the question is whether these techniques are therefore also captured by these parts of Annex I.

2.1.2 Legal interpretative clues

The sole fact that the definition of a GMO in the EU regulatory system has not undergone a substantial change since its redaction in 1990, is in itself not a sufficient argument to conclude that it is not fit for application on organisms obtained through new types of techniques that have been developed after this redaction.

For cases not explicitly mentioned in the GMO definition, as set out in articles 2, 3, Annex IA Part 1, Annex IA Part 2 and Annex IB of Directive 2001/18/EC, an interpretation should be given with regard to the actual text and the intention of the legislator.

In addition, in the EU regulatory system, the intention of the EU legislator itself is bound by primary legislation, i.e. the EU constituting treaties. A legally correct interpretation of the GMO definition therefore also demands that its interpretation is in accordance with EU primary legislation.

The EU GMO definition is a flexible and open definition, allowing a flexible and evolutive
interpretation.\textsuperscript{85}

To trace the intention of the EU legislator and the true extent of the law with regard to the GMO definition in relation to the listed questions, the thesis will look for legal interpretative clues.

\textbf{2.1.3 Interpretative indications in the law and other binding legal documents}

Before turning to interpretative opinions by jurisprudence and doctrine, the law itself should be consulted in an effort to find clarification for the listed questions. The law is namely the first authority with regard to its own interpretation.

Directive 2001/18/EC, and all other EU legislative documents covering “GMOs”\textsuperscript{86} for that matter, do not explicitly elaborate on this GMO definition.

Articles 2, 3, Annex IA Part 1, Annex IA Part 2 and Annex 1B of Directive 2001/18/EC are the key provisions with regard to the GMO definition for the ensemble of GMO legislation, and there are no supplementary provisions explicitly touching on this definition. Neither in Directive 2001/18/EC, nor in the other abovementioned relevant legislative documents.

Firstly, the list of definitions in article 2 of Directive 2001/18/EC does not contain further specific definitions with regard to the terms used to define “GMO” in article 2(2). Only the term “organism” is explained.\textsuperscript{87}

The terms “…altered in a way…”, “heritable material”, and “recombinant nucleic acid molecules” remain undefined in the law.\textsuperscript{88}

Furthermore, the other annexes in the GMO directives and regulations do not touch on the GMO

\textsuperscript{85} In a way, it could be argued that the EU legislator in fact did anticipate future scientific developments in its regulatory system for modern biotechnology by redacting a definition for a key scope term that leaves room for interpretation, refer to the introduction to this thesis.

\textsuperscript{86} As defined in Directive 2001/18/EC.

\textsuperscript{87} Cf. supra Article 2(1) of Directive 2001/18/EC

\textsuperscript{88} In addition, among others the terms "in vitro fertilisation", "conjugation", "transduction", "transformation", "polyploidy induction" and "mutagenesis" in Annex IA Part 2 and Annex IB of Directive 2001/18/EC remain undefined. The evaluation of these terms however escapes the scope of this thesis.
definition either.
They touch –among others– on the implementation of the prescribed environmental risk assessment in authorization procedures under Directive 2001/18/EC, information requirements for notifications under Directive 2001/18/EC, duties and tasks of the community reference laboratoria under Regulation (EC) No 1829/2003, information requirements in notification procedures under Regulation (EC) No 1946/2003, but not on the interpretation or implementation of the terms in the definitions list in article 2, the scope exemption in article 3 or the provisions in Annex IA Part 1, Annex IA Part 2 and Annex 1B of Directive 2001/18/EC.

In conclusion, articles 2, 3, Annex IA Part 1, Annex IA Part 2 and Annex 1B of Directive 2001/18/EC are the only explicit provisions in the law outlining the GMO notion.

Notwithstanding the absence of supplementary explicit interpretative provisions in the law with regard to the GMO definition, some implicit indications could be derived from the larger context of the law.
This larger context comprehends, but is not necessarily limited to, the entirety of the text, i.e. operational as well as non-operational provisions, the coherence of the considered provisions with other parts of the text, the coherence of the considered provisions with other relevant documents, the coherence of the considered provisions with the entire EU regulatory system as well as with international treaties and the underlying legislative motives and objectives and historic antecedents leading to the redaction of the considered provisions.
The logical implementation and the consequences of the application of a certain interpretation of the law in practice should lastly be considered as well.

A subsequent chapter on the interpretation of the EU law by the European Court of Justice will list and outline the possible interpretative indications and methods used to explain EU law.

In addition to the text and the larger context of the law, other binding legal documents, guidelines and official communications drawn up by the legislator could shed some light on the listed questions.

89 Annex II of Directive 2001/18/EC
90 Annex III A and B of Directive 2001/18/EC
91 Annex of Regulation (EC) No 1829/2003
93 See: subchapter 2.1.7.
Since the establishment of the regulatory framework on GMOs in 1990, the EU legislator has issued a number of official guidance documents with regard to the implementation and interpretation of this framework by the member states. These guidance documents correspond to the EU objective of an extensive harmonisation in the implementation, application and interpretation of the EU regulatory framework for GMOs by the member states.

With regard to the interpretation of the legal definition of “GMO” and the application of the definition on the organisms produced through the New Breeding Techniques, the EU Commission and the EU legislator have nonetheless so far remained silent in their communications linked to GMO legislation.

The European Commission has issued official guidelines on technical guidance for sampling and detection of GMOs\(^{94}\), on guidelines for the development of national coexistence measures to avoid the unintended presence of GMOs in conventional and organic crops\(^{95}\) and on standard reporting formats for presenting the monitoring results of the deliberate release into the environment of GMOs, as or in products, for the purpose of placing on the market, pursuant to directive 2001/18/EC\(^ {96}\), but none of these touch on the extent of the GMO definition nor on the application of the definition on New Breeding Techniques.

The EU legislator nor the EU Commission have so far not addressed the regulatory status of the organisms produced through the New Breeding Techniques in any communication regarding the regulation of GMOs.\(^ {97}\)

### 2.1.4 Jurisprudence and administrative decisions

In absence of (explicit) interpretative indications in the text of the law and in other binding legal communications by the legislator, interpretative opinions by jurisprudence and administrative authorities might offer a clarifying outlook.

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\(^{94}\) Commission Recommendation 2004/787/EC  
\(^{95}\) Commission Recommendation 2010/01/EC  
\(^{96}\) Commission Decision 2009/770/EC  
\(^{97}\) As stated before, the EU is still assessing the safety aspects of New Breeding Techniques through the European Food Safety Authority (EFSA).
In the field of EU biotechnology law however, this is not self-evident.

So far, there have been very few cases before the European Courts that touch on the extent of the definition of "GMO" as set out by article 2, 3 and the relevant parts of Annex I of Directive 2001/18/EC.

Most noteworthy is Karl Heinz Bablok and Others v Freistaat Bayern, in which the European Court of Justice ruled that honey containing pollen from genetically modified maize is subject to the authorisation procedure under Regulation (EC) No 1829/2003 when placed on the market. Nevertheless, the Court ruled that the pollen themselves could not be qualified as GMOs. While it was not contested that they contained foreign DNA, it was clear that as an ingredient in the honey, they were not able to reproduce and thus to pass this genetic material on. Therefore, the Court found that the pollen were not captured by the legal definition of an "organism" and as a result could not be qualified as a genetically modified organism either.

While the pollen themselves were not qualified as GMOs, the Court ruled the honey to be captured by Regulation (EC) No 1829/2003. The Court found that the pollen were produced from a GMO, as they were derived from the genetically modified maize.

As such, the honey (and the pollen therein) was to be qualified as "food … containing ingredients produced from GMOs", falling under article 3(1) (c) of said regulation.

A noteworthy consideration that can be derived from this jurisprudence is that the capacity of an organism of replication or of transferring genetic material (cf. Article 2(1) of Directive 2001/18/EC) must not only be subjectively evaluated vis-à-vis the organism itself, but also objectively in the light of the circumstances.

While, as mentioned, only the EU lawmaker and the European Court of Justice can make binding

98 Case C-281/11 Commission v Poland, In which the Republic of Poland had been brought before the Court for an alleged wrongful transposition of -among others- the GMM definition. The case has however little to no relevance for the survey in this thesis.
99 Case C-442/09 Karl Heinz Bablok and Others v Freistaat Bayern
100 Articles 5-7
101 "any biological entity capable of replication or of transferring genetic material", Article 2(1) of Directive 2001/18/EC
102 Consideration 62 of the dictum reads: "The answer to the first question is therefore that the concept of a GMO within the meaning of Article 2.5 of Regulation No 1829/2003 is to be interpreted as meaning that a substance such as pollen derived from a variety of genetically modified maize, which has lost its ability to reproduce and is totally incapable of transferring the genetic material which it contains, no longer comes within the scope of that concept."
statements on the interpretation of EU law, it is nonetheless relevant to examine how the New Breeding Techniques and their derived organisms are viewed by the EU authorities involved in the authorization of the products obtained through the use of the New Breeding Techniques.

The authorisation procedures for the placing on the market of GMOs under articles 12-24 of Directive 2001/18/EC fall under the exclusive competence of the authorities of all the EU member states. As most of the NBTs and the derived products are still at a development stage, there have so far been no requests for the authorisation of the placing on the market of these products.  

The same, a fortiori, applies for the authorization under Regulation (EC) No 1829/2003 for food and feed products obtained through the use of NBTs: there are no procedures completed or pending.  

It is also relevant to examine how the New Breeding Techniques and their resulting organisms are viewed in the regulatory systems of the member states.

The authorisation procedure for the experimental release (e.g., field trials) of GMOs in the environment under articles 5-11 of Directive 2001/18/EC falls under the competence of the administrative authorities of the member states. So far, there have been little to no national administrative decisions authorising the experimental release of plants developed through the use of NBTs.

103 Refer to the EU Register of authorised GMOs: http://ec.europa.eu/food/dyna/gm_register/index_en.cfm
104 Idem.
105 Refer to the Joint Research Center of the Commission's register for notifications of the deliberate release into the environment of GM plants for any other purposes than placing on the market (experimental releases): http://gmoinfo.jrc.ec.europa.eu/gmp_browse.aspx
The register contains a number of notifications for the experimental release of so-called cisgenic plants. However, in most, if not all cases, these plants also contained transgene material in the form of marker genes or i-DNA borders. For that reason, there is no doubt that these plants were GMOs. e.g. Field trial with "cisgenic" late blight resistant potatoes in Belgium: http://gmoinfo.jrc.ec.europa.eu/gmp_report.aspx?CurNot=B/BE/10/V1; Field trial with "cisgenic" barley with improved phytase activity in Denmark: http://gmoinfo.jrc.ec.europa.eu/gmp_report.aspx?CurNot=B/DK/12/01; Field trial with "cisgenic" scab resistant apples in the Netherlands: http://gmoinfo.jrc.ec.europa.eu/gmp_report.aspx?CurNot=B/NL/10/05.
The German government has on 05/02/2015 stated that the experimental release of a herbicide tolerant rape, produced through ODM, is not subject to the requirements in Directive 2001/18/EC. The Budesamt für Verbraucherschutz und Lebensmittelsicherheit both argues that the plant is not a GMO, and that the plant is exempted from the GMO legislation as it is produced by mutagenesis. Refer to: http://www.testbiotech.org/sites/default/files/BVL%20Cibus.pdf
106 Due to the succinctness of the information supplied by the notifiers and/or the operator of the database with regard to the technique(s) used, it was not possible to identify additional applications and authorisations for field trials in which NBTs may have been used.

32
Lastly, the authorisation procedure for the contained use of class 3 and 4\textsuperscript{107} GMMs under Directive 2009/41/EC falls under the exclusive competence of the administrative authorities of the member states.

While it is clear that NBTs and their derived organisms are on a regular basis used in European laboratories, it is not self-evident to access permits granted for this contained use. The summaries of the permits listed in the national databases are too succinct to identify which technique exactly is used. In addition, the applicant and/or competent authority are often not required to disclose this type of information under the national regulatory framework.\textsuperscript{108}

### 2.1.5 Doctrine

Doctrine on (EU) biotechnology law in general is scarce.

It is a relatively young and technical field of law, regulating a relatively young and technical field of science. Therefore, legal writing about biotechnology law not only requires an in-depth understanding of environmental law, but also an in-depth understanding of the scientific techniques of modern biotechnology and the practice of genetic modification.\textsuperscript{109}

While there is no shortage of introductory and/or general legal scriptures, \textit{de lege lata} as well as \textit{de lege ferenda}, on the whole of EU GMO legislation\textsuperscript{110}, interpretative doctrine on specific and/or technical provisions in this legislation remains minimal.

It comes therefore to no surprise that doctrine specifically elaborating on the extent of the legal definition of "GMO", which is of a technical nature, and, \textit{a fortiori}, its application on New Breeding Techniques, is nonexistent.\textsuperscript{111}

\textsuperscript{107} As mentioned before, Directive 2009/41/EC is an environmental directive, and therefore sets minimum standards for the member states.

\textsuperscript{108} Moreover, the operators of these databases themselves are imposed by the same problem. Upon contact, they cannot provide any quantitative information. The operators of the databases of Belgium, The Netherlands and The United Kingdom have been contacted.

\textsuperscript{109} Human sciences meet exact sciences, so to speak.


\textsuperscript{111} In this context it should be noted that the abovementioned expert reports by the NTWG, COGEM, ZKBS, ACRE,
2.1.6 Lack of legal clues: What now?

As the EU legislator and the EU Commission have so far not addressed the legal questions linked to the application of the GMO definition on the organisms obtained through NBTs, it is currently impossible to draw definite conclusions with regard to the current regulatory status of these organisms in the EU. In addition, it is not possible to predict how, when, and even if the legislator will intervene: this is a matter of policy.

Furthermore, the fact that neither the administration, nor jurisprudence, nor legal doctrine offer a satisfying solution to the current legal issues at hand, raises the question: how should the EU law be interpreted then?

Neither the treaties establishing the European Union, nor secondary EU law contain explicit provisions that deal with the interpretation of the EU law in general.112 In other words, there is no explicit, general legal basis addressing the interpretation of the EU law.

Article 19 of the Treaty on the European Union does however confer the competence to interpret the EU law to the European Court of Justice.113 Since its establishment in 1952, the Court has built up a vast record of explanatory jurisprudence with regard to EU legislation.

As stated before, the European Court of Justice has so far not formulated an opinion with regard to the regulatory status of the organisms obtained through New Breeding Techniques. More in general, the Court’s jurisprudence on the definition of “GMO”, as set out in Directive 2001/18/EC, is minimal.

In absence of an intervention by the EU legislator, the Court however remains the only official

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BREYER et al., HUSBY… should probably not be considered “doctrine”: these reports assess the abovementioned unclarities and/or regulatory status of NBTs on mostly technical and scientific arguments, not really, or only to a very limited extent on legal arguments.

The abovementioned report prepared by the NBT Platform (private stakeholders) does consider a number a legal arguments. It is not sure if this report should be considered “doctrine”, though.

112 ITZCOVICH, G., The Interpretation of Community Law by the European Court of Justice, German Law Journal, p. 539
113 As well as to “…the General Court and specialised courts…”
instance that could give a binding legal opinion on the current legal status of the organisms obtained through NBTs in the light of the EU law.

In absence of clarifying jurisprudence by the European Court of Justice, this thesis can only make a reasoned prediction as to what the Court could or would say on the discussed questions.

In order to make a credible attempt to predict what the European Court of Justice would say on the above discussed issues, the Court’s interpretative methods should be examined and outlined.

### 2.1.7 Interpretation of the EU law by the European Court of Justice

When dealing with ambiguities in the EU law, The European Court of Justice - in its own words – generally considers "the spirit, the general scheme and the wording"\textsuperscript{114} of a provision.

In practice, the Court relies on a wide range of possible interpretative methods, which have amply been described in legal doctrine.\textsuperscript{115}

Before turning to any other interpretative criteria, the Court considers the literal reading ("the wording") of the text of the law. In practically all cases where the Court is asked to explain Union law, the linguistic interpretation of the wording will be the starting point: the literal meaning of the law is assumed to be the correct meaning of the law.

The Court's method is in this context very straightforward: it simply draws a conclusion based on the normal meaning of the words used.\textsuperscript{116,117}

When the linguistic interpretation is in itself sufficient to be conclusive with regard to a considered ambiguity, it will in many cases prevail over any other method of interpretation: \textit{in claris non fit interpretatio}.

\textsuperscript{114} Case C-26/62 Van Gend en Loos v Nederlandse Administratie der Belastingen; Case C-6/64 Costa v ENEL

\textsuperscript{115} With regard to the three "basic" interpretative methods, the authoritative classification by J. Bengoetxea will be followed here: BENGOTEZEA, J., \textit{The legal reasoning of the European Court of Justice: Towards a European Jurisprudence}, 1993, p. 234-270

\textsuperscript{116} See e.g. Case C-376/98 Germany v Parliament and Council (83); Case C-326/99 Stichting 'Goed Wonen' v Staatssecretaris van Financiën (45); Case C-438/99 Jimenez Melgar v Ayuntamiento de Los Barrios (50)

\textsuperscript{117} A commonly applied form of literal interpretation is the comparison of a considered ambiguity in a provision with the corresponding provision in a different language version of the EU law.

Refer to: CAPETA, T., "Multilingual law and judicial interpretation in the EU", in SOCANAC, L., "Curriculum, Multilingualism and the Law" Nakladni zavod Globus, 2009, p. 1-17
Notwithstanding a clear and understandable wording of the text, the Court has argued that an interpretation based on other criteria is warranted if the literal meaning of the text is in conflict or inconsistent with the context and/or the spirit of the law.\footnote{118 See e.g. Case C-9/70 Grad v Finanzamt Traunstein (12-14); Case C-173/88 Skatteministeriet v Morten Henriksen (11)}

When the wording of a considered text is in itself not conclusive, or whenever the Court sees reason to depart from the purely literal interpretation of the text, the Court will resort to systemic criteria (\textit{the general scheme}) in order to explain the EU law.

This implies in essence the evaluation of the coherence of the considered provision with its normative context. This normative context not only comprehends titles and recitals\footnote{119 See e.g. Case C-255/99 Anna Hummer (48) – reference to a title; Case C-293/98 Entidad de Gestión de Derechos de los Productores Audiovisuales v Hosteleria Asturiana SA (15-22) – reference to recitals; Case C-348/98 Mendes Ferreira v Companhia de Seguros Mundial Confi﬈naﬂ SA (24-25) – reference to recitals} and provisions\footnote{120 See e.g. Case C-434/98 P Council v Silvio Busacca (24); Case C-66/99 Wandel v Hauptzollamt Bremen (47); Case C400/00 Club-Tour, Viagens e Turismo SA v Goncalves Garrido (15)} of the same legal text, but also relevant provisions\footnote{121 See e.g. Case C-275/95 Unitron Scandinavia A/S and others v Ministeriet for Fodevarer, Lanbrug og Fiskeri} of other legislation.

An unclear provision is often also considered in the light of written and unwritten general principles and concepts prevalent in the entire EU regulatory system.\footnote{122 See e.g. Case C-186/87 Cowan v Le Trésor public (17) – principle of non-discrimination on the grounds of nationality; Case C-117/01 KB v National Health Service Pensions Agency and Secretary for Health – principle of non-discrimination on the ground of sex; Case C-508/10 Commission v Netherlands – principle of \textit{effet utile}; In Case C-377/98 Kingdom of the Netherlands v Parliament and Council the Court evaluated Directive 98/44/EC on Biotechnological inventions in the light of the principle of subsidiarity} The underlying assumption here is that legal provisions in the same legal text should be consistent with one another, and should be consistent with the whole of EU law, and they should be interpreted accordingly.

It is in a sidenote important to consider here that the entire EU legal system is structured in a hierarchical order.

The EU constituting treaties\footnote{123 Treaty on the European Union (TEU) and the Treaty on the Functioning of the European Union (TFEU). The Charter of Fundamental Rights is since the Treaty of Lisbon (2009) also considered 'primary legislation'.} form as 'primary legislation' the pinnacle of this order. Secondary legislation and implementing or delegated legislation are situated under the constituting treaties, and have a subordinate position. International agreements concluded by the EU under article 216 TFEU have an important but particular position in this order: while they are considered as secondary legislation, and are therefore situated under the constituting treaties, they have a greater hierarchical
value than the unilateral secondary legislation.\textsuperscript{124}\textsuperscript{125}

This hierarchical order is reflected in the systemic interpretation of the EU law: secondary legislation must comply with – and is therefore to be interpreted in a way that it is consistent with the principles and provisions in the Treaty on the European Union (TEU) and the Treaty on the Functioning of the European Union (TFEU). Different measures of secondary legislation that are situated on the same hierarchical level however, should be interpreted in a way that they are consistent with each other for the sake of the coherence of the entire legal system: words and concepts should be given the same meaning in the entire system, unless there is a reason why not to.\textsuperscript{126} Different measures of secondary legislation that are situated on a different hierarchical level should be interpreted in a way that the subordinate/implementing measure complies with the superior measure /the measure that it implements.

The third and last base group of interpretative criteria the Court resorts to, are the dynamic criteria ("the spirit"). Bengoetxea\textsuperscript{127} and Beck\textsuperscript{128} distinguish three subgroups of dynamic criteria: teleological, functional and consequentialist criteria. These criteria often operate jointly, reinforcing one another, and are aimed at a dynamic and evolutive appreciation of the law.

Teleological criteria\textsuperscript{129} are aimed at the understanding of the law in function of its underlying objective and the underlying objective of its normative context. These objectives may be identified in the law itself, as well as in other legal documents that together form the normative context of the law.

Functional criteria\textsuperscript{130} are aimed at the interpretation of the law that warrants its most effective and efficient influence. They correspond to the principle of \textit{effet utile}, or the doctrine of "effectiveness".

\begin{itemize}
\item \textsuperscript{124} Cf. Article 216(2) TFEU: "Agreements concluded by the Union are binding upon the institutions of the Union and on its Member States."
\item \textsuperscript{125} Joined Cases C-402/05 P and C-415/05 P Kadi v Council & Commission; Case C-61/94 Commission v Germany; Case C-90/92 Dr Tretter v Hauptzollamt Stuttgart-Ost
\item \textsuperscript{126} BECK, G., The legal reasoning of the Court of Justice., 2012, p. 193
\item \textsuperscript{127} BENGOTXEA, J., The legal reasoning of the European Court of Justice: Towards a European Jurisprudence, 1993
\item \textsuperscript{128} BECK, G., The legal reasoning of the Court of Justice., 2012, p. 207-215
\item \textsuperscript{129} See e.g. Case C-245/01 RTL Television gmbH v Nudersächsiche Landesmedienanstalt für privaten Rundfunk (62); Case C-162/09 Secretary of State for Work and Pensions v Taous Lassal
\item \textsuperscript{130} See e.g. Case C-187/87 Saarland v Ministère de l'Industrie (19); Case C-453/99 Courage Ltd v Crehan (26); Case C-109/00 Tele Danmark A/S v Handels- og Kontorfunktionserernes Forbund i Danmark (HK) (29); Case C-212/00 Stallone v Office national de l'emploi (22)
\end{itemize}
They are closely connected with the teleological criteria, in that sense that the law's effective influence has to be consistent with the purpose of the law.

Consequentialist criteria\textsuperscript{131} lastly assume that the law must be interpreted in a way that has regard for the foreseeable legal and factual consequences of said interpretation.

In addition to the above three base groups of interpretative criteria, a number of additional\textsuperscript{132} interpretative criteria can be distinguished, to which the Court resorts to or has resorted to when dealing with ambiguities in EU law. These additional criteria often (partly) overlap with, and are sometimes indistinguishable from the classic criteria. They are nonetheless worth mentioning here.

A commonly distinguished additional group of arguments are the genetic and historical criteria.\textsuperscript{133} Both not always clearly distinguishable from each other, the genetic criteria prescribe to interpret the legal provisions in a way corresponding to the will of the legislator, while historic criteria prescribe to interpret legal provisions in the context of the historic events preceding and accompanying the legislative initiative.

These criteria may be found in (preparatory) documents, in which the legislator has communicated his intentions, as well as in the law itself and its normative context. Historic arguments may be found in non-legal sources.

With regard to the genetic criteria, Itzcovich makes the valid remark that a certain caution has to be taken into account in applying them: secondary Union legislation is often the fruit of a complex process of preparatory negotiation based on diverting political, economic, scientific, and other interests in which a plurality of (political) actors partake.

The will of the EU legislator may not always be distilled from a prima facie interpretation of preparatory documents such as the published *travaux préparatoires*. Instead, these documents will often represent "an incoherent and inconclusive plurality of viewpoints and opinions".\textsuperscript{134} Moreover, it could be argued that these documents represent a mere snapshot in time of the legislative process and do not serve a dynamic and evolutive interpretation of the EU law.

\textsuperscript{131} See \textit{e.g.} Case C-43/75 Defrenne \textit{v} SABENA (p. 460 (e)); Case C-6/90 Francovich \textit{and} Bonifaci \textit{v} Italy; Case C-26/62 \textit{Van Gend en Loos v Nederlandse Administratie der Belastingen}.

\textsuperscript{132} With regard to the additional interpretative methods, the classification used by G. Beck will be followed here: \textit{BECK, G., The legal reasoning of the Court of Justice.}, 2012, p. 215-224.

\textsuperscript{133} See \textit{e.g.} Case C-310/90 Nationale Raad van de Orde van Architecten \textit{v} Egle (12); Case C-2/74 Reyners \textit{v} Belgium; Case C-578/08 Chakroun \textit{v} Minister van Buitenlandse Zaken.

\textsuperscript{134} \textit{ITZCOVICH, G., The Interpretation of Community Law by the European Court of Justice, German Law Journal, p. 554.
The Court itself has on multiple occasions expressed a certain reluctance to (only) rely on preparatory documents in order to explain EU law.\textsuperscript{135} On other occasions, the Court has relied on these documents as supporting arguments to confirm a certain interpretation of a provision based on other criteria.\textsuperscript{136}

To sum up, it is important to note that the Court maintains a balanced approach when relying on \textit{travaux préparatoires} in order to explain EU law: while the Court does on occasion rely on these documents as supporting guidance to interpret a given rule, the significance of these documents in the Court's reasoning in general should be put in perspective.

Furthermore, the Court sometimes relies on comparative criteria in order to formulate an explanation for an obscurity in the EU Law. Largely overlapping with the systemic criteria, these criteria seek to find clarification in national\textsuperscript{137} (member states) and international\textsuperscript{138} (treaties) legal systems. However, given the autonomous nature of the European Union and EU law, the Court is rather reluctant\textsuperscript{139} to apply these.

Special legal criteria include analogical and \textit{a fortiori} arguments, \textit{a contrario} and \textit{ad absurdum} arguments. They also include the \textit{lex specialis - lex superior} argument. They are applied when it is not sure if a particular provision is applicable to a certain situation.

\textit{Analagical and \textit{a fortiori}}\textsuperscript{140} arguments extend the scope of a written or unwritten rule to a situation that is not explicitly covered by said rule.

The Court not only resorts to analogical criteria via the application of precedents (analogical application of a preceding jurisprudence), but also via the expansion of the scope of written provisions\textsuperscript{141}, albeit with a certain reluctance.

\textsuperscript{135} See e.g. Case C-2/74 Reyners v Belgium; Case C-292/89 The Queen v Immigration Appeal Tribunal, ex p Antonissen (18)
\textsuperscript{136} See e.g. Case C-162/09 Secretary of State for Work and Pensions v Taous Lassal; Case C-45/01 Christoph-Dornier-Stiftung für Klinische Psychologie v Finanzamt Gießen; Case C-133/00 Bowden and Others v Tufnels Parcels Express Ltd (42); Case C-310/90 Nationale Raad van de Orde van Architecten v Egle (12)
\textsuperscript{137} See e.g. Case C-159/90 Society for the Protection of Unborn Children Ireland Limited (SPUC) v Grogan and Others; Case C-36/02 Omega Spielhallen v Oberbürgermeisterin der Stadt Bonn
\textsuperscript{138} See e.g. Case C-4/73 J. Nold, Kohlen-und Baustoffgroßhandlung v Commission of the European Communities – referral to the ECHR; Case C-112/00 Eugen Schmidberger v Republik Österreich (71) – referral to the ECHR
\textsuperscript{139} See e.g. Case C-51/76 Verbond van Nederlandse Ondernemingen v Inspecteur der Invoerrechten en Accijnzen; Case C-372/82 Ekro BV Vee- en Vleeshandel v Productschap voor Vee en Vlees; Case C-149/85 Wybot v Faure (12); Case C-102/86 Apple and Pear Development Council v Commissioners of Customs and Excise
\textsuperscript{140} See e.g. Case C-99/00 Criminal proceedings against Kenny Lyckeskog; Case C-210/06 Cartesio Oktákó és Szelgúntató Bt.; Case C-200/07 Alfonso Luigi Marra v Eduardo De Gregorio
\textsuperscript{141} See e.g. Case C-152/09 André Grootes v Amt für Landwirtschaft Parchim (64); Case C-28/91 Haneberg v BALM (22-25)
In Krohn\textsuperscript{142} the Court has established its doctrine on the analogical application of written provisions of EU law:

13. It must be pointed out that the scope of a regulation is normally defined by its own terms and it may not in principle be extended to situations other than those which it envisaged.

14. However, as the Court has decided in its judgments of 20 February 1975 (Adolf Reich v Hauptzollamt Landau (1975) ECR 261) and 11 July 1978 (Union Française des Cereales v Hauptzollamt Hamburg-Jonas (1978) ECR 1675), the position may be different in certain exceptional cases. It is clear from those judgments that traders are entitled to rely on an application by analogy of a regulation which would not normally be applicable to them if they can show that the rules applicable to their case:

on the one hand, are very similar to those which it is sought to have applied by analogy; and,

on the other hand, contain an omission which is incompatible with a general principle of Community law and which can be remedied by application by analogy of those other rules."

To sum up, the Court prescribes two necessary requirements in order to apply the EU rule by analogy: the rule that would normally be applicable to a given situation 1) is very similar to the one that is sought to be applied by analogy and 2) contains an omission that is incompatible with a general principle of Community law and which can be remedied by application by analogy of that other rule.

\textit{A contrario} and \textit{ad absurdum} arguments limit the scope of a certain provision by determining that a certain situation is not captured.

The application of an \textit{a contrario} argument implies in essence the deduction that a given situation is not covered by a certain rule because that rule does not \textit{expressis verbis} target that situation.

Again the Court is reluctant to accept and apply \textit{a contrario} argumentation. In its Meroni\textsuperscript{143} jurisprudence the Court strongly limits the admissibility of this argument: "...an argument in reverse is only admissible when no other interpretation appears appropriate and compatible with the provision and its context and with the purpose of the same."

In accordance with this jurisprudence, the Court consistently rejects \textit{a contrario} argumentation when

\textsuperscript{142} Case C-165/84 Krohn v BALM (13-14)

\textsuperscript{143} Case C-9/56 Meroni & Co Industrie Metallurgiche SpA v High Authority (140)
this is not supported by supplementary interpretative arguments.\(^{144}\) (\(e.g.\) systemic or dynamic arguments)

Only rarely\(^{145}\) the Court accepts this argument, when it is sufficiently supported by supplementary interpretative indications.

The application of an \textit{ad absurdum} argument implies in essence the observation that the application of a certain rule to a given situation would lead to unacceptable or absurd consequences. This argument largely – if not completely – corresponds to the abovementioned consequentialist criteria.

The \textit{lex specialis - lex superior} argument\(^{146}\) is applied when two provisions contradict each other: the more specific provision prevails over the more general one.

A very last group of supplementary interpretative criteria the Court resorts to, are, what best can be summarized as practical arguments. They comprehend legal dogmatic, empirical and general practical arguments.

Legal dogmatic arguments involve the logical analysis of legal concepts and propositions and the application of this analysis and its results on an unclear law.

Empirical arguments involve the analysis of legal concepts and propositions based on empirical assumptions and findings and the application of this analysis and its results on an unclear law.

General practical arguments lastly, are elements of rational argumentation that supplement the legal argumentation.

It should in conclusion be reiterated that the distinction between all the above criteria and arguments is not always clear, and they will in many cases overlap with one another. They operate jointly and reinforce each other. This goes for the traditional as well as the additional interpretative criteria and arguments.

It should lastly be noted that, when resorting to all the above criteria and arguments discussed here, the Court retains a large amount of discretion, even to the point where the Court is said to play an almost political role with regard to EU legislation.

Moreover, there is no strict methodology recognisable in the Court's application of these criteria and arguments.

\(^{144}\) See \textit{e.g.} Case C-229/09 Hogan Lovells International \textit{v} Bayer CropScience (31); Case C-49/09 Commission \textit{v} Poland (34); Case C-378/08 \textit{ERG and Others v Ministerio dello Sviluppo economico} (37); Case C-446/07 \textit{Severi \textit{v} Regione Emilia Romagna} (47-48)

\(^{145}\) Case C-434/08 \textit{Harms \textit{v} Heidinga} (44)

\(^{146}\) See \textit{e.g.} Case C-582/08 \textit{Commission \textit{v} UK}; Case C-27/02 \textit{Petra Engler \textit{v} Janus Versand GmbH}
arguments. The (relative) priority of the linguistic interpretation seems to be the only exception to this rule.

As a result of this large margin of appreciation, the outcome of the Court's interpretative activities is per definition not entirely predictable.

Based on the above interpretative "scheme", the thesis will hereafter discuss the most pressing questions in the legal GMO definition.

The thesis will primarily focus on the issues linked to the terms "...altered in a way...". These terms are the pivotal terms in the EU GMO definition, and therefore also entail the key discussion in the debate with regard to the regulatory status of plants produced through NBTs.

Some of the other identified discussions entail complex technical questions, which in turn entail legal questions. The survey and analysis of these questions exceed the scope of this thesis. Therefore, the discussions with regard to the terms "heritable material" and the regulatory status of a GMO offspring will only briefly be examined and/or touched on, but may be explored in a next paper.

The discussion on the legal implications of a transient expression and presence of a genetic alteration has been highlighted above, and will hereafter not be evaluated.

It will in any case be evaluated if, and if so, how the conclusions with regard to the "...altered in a way..." discussion reflect in the other identified discussions.

2.1.8 "...altered in a way..."

A focus on the process, the product, or both?

The terms "...altered in a way..." in article 2(2) of Directive 2001/18/EC could refer to a resulting organism that contains a genetic "alteration" (emphasis on the product), to the technique or process

147 e.g. The technique of ZFN-2 introduces, in addition to a zinc finger nuclease construct, a repair template in a targeted organism. It is not clear if this repair construct can be considered "heritable material" in the sense of the law.
of genetic "alteration" to which a resulting organism has been subject (emphasis on the technique/process), or to a resulting organism that contains a genetic "alteration" as a result of the use of a technique or process of genetic "alteration" (emphasis on both the product and the technique/process).

The wording of article 2(2)

A strict linguistic interpretation of the wording of the terms "...altered in a way..." is in itself not entirely conclusive with regard to whether the product-based interpretation, the process-based interpretation or the combined interpretation should be followed. However, the phrasing "altered in a way...that does not occur..." itself seems to refer to a change in a state or a result, rather than to the application of a process or a technique. Something that has been "altered" is something that has been changed or made different.148

It will hereafter be evaluated if, and to what extent this emphasis on the result is supported by the purpose and the general scheme of the law.

The general scheme and the purpose of article 2(2): a focus on the process

It is first of all undeniable that the EU legal GMO definition places a heavy emphasis on techniques and processes giving rise to an "altered" organism. This can directly be derived from the text of the law.

Article 2(2)(a) states: genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1." Therefore, the law explicitly establishes the use of a technique of genetic modification as a minimum and necessary requirement in order for an organism to be legally qualified as a GMO.

In addition, the wording in this provision is clear, so there is currently no reason to divert from the literal meaning of this provision: in claris non fit interpretatio.

Furthermore, a noteworthy consideration in the explanatory memorandum149 accompanying the initial

Commission proposal for Directive 90/220/EC on page 5 reads: *The present approach, which focusses on the new techniques of genetic engineering, is the first and most urgent step in the regulatory process; however, this will not impede evolution towards a more organism-related approach. Thus, the Commission will, as experience and knowledge on the matter build-up (sic), undertake to regulate the release of certain categories of naturally-occurring organisms, such as known human, plant or animal pathogens, and non-indigenous organisms. Moreover, different categories of organisms and/or techniques may be established....*" 

In this consideration, the Commission *expressis verbis* states that the regulatory framework for GMOs focusses at least on techniques. The use of a technique of genetic modification is therefore an essential, *i.e.* constitutive element in the EU GMO definition.

In a first provisional conclusion, "*...altered in a way..." for the above reasons [at least] refers to the use of a technique of genetic modification, as listed in Annex IA Part 1 of Directive 2001/18/EC, and therefore the use of one of these techniques is a constitutive element in the EU GMO definition."

An interpretation of the terms "*...altered in a way..." that has no regard for the techniques used to modify an organism, *i.e.* the strictly product-based interpretation, is currently legally not defendable for the simple reason that such an interpretation is in straight contradiction with the text of the law and the initial intention of the legislator.

*The general scheme and the purpose of article 2(2): a focus on the product*

The next question is whether there is also a focus on the product or result of the use of these techniques.

This question should be answered affirmatively. It appears that the GMO definition also relies on the novelty of the resulting organism, *i.e.* the novelty of its genetic material, as a result of the use of techniques and processes.

This novelty is reflected in the formation of (a) new combination(s) of genetic material in the organism. A new combination of genetic material is established by the presence of ‘new’ genetic material in the organism's genome or the alteration or deletion of (a) gene(s) in the original genetic material of the organism.

This can be concluded derived from Annex IA Part 1, which enumerates the techniques that give rise
to a GMO in the sense of the law:

Indent (1) of Annex IA Part 1 mentions: "... involving the formation of new combinations of genetic material...".

Indent (3) of Annex IA Part 1 mentions: where live cells with new combinations of heritable genetic material are formed through the use...

In addition, the travaux préparatoires\textsuperscript{150} to Directive 90/219/EC and Directive 90/220/EC\textsuperscript{151} provide supplementary supportive indications for the requirement of the formation of (a) new combination(s) of genetic material in the organism.

Article 1 (b) of the initial Commission proposal preceding Directive 90/219/EC\textsuperscript{152} defines a genetically modified organism as: "any organism derived from the formation of a new combination of genetic material by the insertion of nucleic acid molecules produced by whatever means outside the cell, into any virus, bacterial plasmid or other vector system so as to allow their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation".

While the co-legislators, i.e. the European Parliament and the Council, did not adopt this definition\textsuperscript{153}, and opted for the above annex-based definition, it could be of an indicative nature as to what the underlying legislative thought is with regard to the constitutive elements that give rise to a GMO.

Whereas the abovementioned consideration in the explanatory memorandum accompanying the initial Commission proposal preceding Directive 90/220/EC recognises a focus on techniques in the regulatory system for GMOs, it does not say that this system exclusively focusses on techniques: the above and hereunder listed arguments suggest that there also is a certain focus on the novelty of the organism.

\textsuperscript{150} For the preparatory documents to Directive 90/220/EC, refer to: \url{http://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX:31990L0220}.

\textsuperscript{151} For the preparatory documents to Directive 90/219/EC, refer to: \url{http://eur-lex.europa.eu/legal-content/EN/HIS/?uri=CELEX:31990L0219}.

\textsuperscript{152} Not all of the preparatory documents are accessible online: the General Secretariat of the Council of the European Union provides these upon request. For the non-public documents, the procedure under Regulation (EC) No 1049/2001 must be followed.

\textsuperscript{153} The current GMO definition (largely) originates in these documents: \textit{cf. Supra.}

\textsuperscript{154} COM(88)160final, dating 06/04/'88 and published in the Official Journal of the European Communities on 28/07/88.

\textsuperscript{153} The initial definitions of "genetically modified organism" and "micro-organism" were replaced by one definition of "genetically modified micro-organism" in Directive 90/219/EC.
Moreover, given that this memorandum was redacted 26 (!) years ago, and given that the EU legislator has since then not substantially adapted the definition, despite the scientific advances, this consideration may warrant an evolutive interpretation of the definition towards a more combined approach.  

A last and important systemic argument in support of the combined interpretation of "...altered in a way..." can be found in the GMO (LMO) definition in the Cartagena Protocol on Biosafety (CPB). The EU signed the CPB on 24 May 2000 and ratified it on 27 August 2002. The CPB entered into force on 11 September 2003.

The GMO (LMO) definition can be found in article 3 (g), (h) and (i) of the CPB.

Article 3(g) reads:

"'Living modified organism' means any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology;'

Article 3(h) reads:

"'Living organism' means any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids; '

Article 3(i) reads:

"'Modern biotechnology' means the application of:

a. In vitro nucleic acid techniques, including recombinant deoxyribonucleic acid (DNA) and direct injection of nucleic acid into cells or organelles, or

b. Fusion of cells beyond the taxonomic family,

that overcome natural physiological reproductive or recombination barriers and that are not

\[\text{154 The strictly product-based interpretation is currently not legally defendable (cf. supra)}\]

\[\text{155 https://bch.cbd.int/protocol/background/}\]
First of all, it is apparent that this definition does refer to both the use of biotechnological techniques and the novelty of an organism obtained by the use of these techniques as requirements to be considered an LMO.\footnote{Mackenzie, R., Burhenne-Guilmin, F., La Viña, A. G. M. and Werksman, J. D. in cooperation with Ascencio, A., Kinderlerer, J., Kummer, K. and Tapper, R. (2003), *An Explanatory Guide to the Cartagena Protocol on Biosafety*, IUCN, Gland, Switzerland and Cambridge, UK. XVI +, p. 45 \(156\)}
The text in article 3(g) clearly supports this assumption: "...any living organism that possesses a novel combination of genetic material obtained through the use of modern biotechnology..." whereby modern biotechnology is explained as the application of a number of techniques that are enumerated in article 3(i) a. and b.) (cf. supra)\footnote{Case C-442/09 Karl Heinz Bablok and Others v Freistaat Bayern (55): The Court of Justice herein distills the criteria of both viability and fertility of the organism. \(158\)}

Furthermore, making abstraction of the differences in the legal definitions of the terms "GMO" (Directive 2001/18/EC) and "LMO" (CPB), it is apparent that these terms in essence have the same meaning.

Whereas the distinction between "GMO" and "LMO" lies in the consideration that the term "GMO" could also refer to a non-living, i.e. dead organism, the EU definition of the term "organism" implies that this is "any biological entity, capable of replication or of transferring genetic material."\footnote{The Commission in the explanatory memorandum accompanying the initial proposal for Directive 90/220/EC on page 7 states: "The definition of ‘organism’ encompasses viruses and other subcellular entities as well as higher plants and animals.” \(159\)} The CPB on the other hand defines a "living organism" as "any biological entity capable of transferring or replicating genetic material, including sterile organisms, viruses and viroids."\footnote{cf. infra, footnote 165 \(160\)} The terms "organism" and "living organism" thus in essence have the same meaning.

It is therefore clear that the terms GMO and LMO largely\footnote{cf. infra, footnote 165} correspond in meaning and are synonyms, despite their different wording in the EU and the CPB system.

Not only are the EU and its member states parties to the CPB, the EU has implemented the Protocol in its own legal order by means of Regulation EC (No) 1946/2003.

Article 1 of Regulation EC (No) 1946/2003 reads: "the objectives of this Regulation are to establish a common system of notification and information for transboundary movements of genetically..."


\(158\) Case C-442/09 Karl Heinz Bablok and Others v Freistaat Bayern (55): The Court of Justice herein distills the criteria of both viability and fertility of the organism.

\(159\) CPB Article 3(h)

\(160\) The Commission in the explanatory memorandum accompanying the initial proposal for Directive 90/220/EC on page 7 states: "The definition of ‘organism’ encompasses viruses and other subcellular entities as well as higher plants and animals.”
modified organisms (GMOs) and to ensure coherent implementation of the provisions of the Protocol on behalf of the Community in order to contribute to ensuring an adequate level of protection in the field of the safe transfer, handling and use of GMOs that may have adverse effects on the conservation and sustainable use of biological diversity, taking also into account risks to human health."

Notwithstanding the EU legislator's intention to ensure the coherent implementation of the provisions of the Protocol, Regulation EC (No) 1946/2003 in article 3(2) maintains the EU's own GMO definition as set out by article 2(2) and the relevant parts of Annex I of Directive 2001/18/EC. The Commission motivates this decision in the explanatory memorandum accompanying the proposal for the Regulation:

"The definition of an LMO under the Protocol is largely consistent with the definition of a Genetically Modified Organism (GMO) under Directive 2001/18/EC of 12 March 2001 on the deliberate release into the environment of genetically modified organisms [3]. The genetic modification techniques applicable to each definition under the two instruments are not the same, however, although this is not likely to impinge on operational aspects of the legislation, and "Furthermore, humans are explicitly excluded from the scope of Directive 2001/18/EC but this is not the case for the Protocol although again, this is unlikely to have any operational consequences."

While the Commission recognises differences in the techniques that are covered by both definitions and recognises the difference in the exclusion of human beings, it is apparent that the Commission otherwise deems the definitions to be consistent with each other.

The EU legislator's consideration that these two legal definitions are largely consistent with each other, and the legislator's expressed intention to coherently implement the CPB in the EU's legal order

162 Furthermore, the extensive list of rejected amendments for reasons of inconsistency with the Protocol illustrates the Commission's intention to stick as close as possible to the text of the Protocol; refer to: COM/2002/0578 final - COD 2002/0046 */
163 "'genetically modified organism', or 'GMO', means genetically modified organism as defined in Article 2(2) of Directive 2001/18/EC, excluding organisms obtained through the techniques of genetic modification listed in Annex IB to Directive 2001/18/EC"
165 The Commission seems to refer to the difference in the regulatory approach for cell fusion. Under the CPB, organisms obtained through "fusion of cells beyond the taxonomic family" that do not "overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection" (art. 3(i) b.) do not meet the LMO definition because the technique is not considered a technique of "modern biotechnology". Under Directive 2001/18/EC, "cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding methods" (Annex IB (2)) is however considered a technique of "genetic modification", and therefore, this technique may give rise to a GMO. Nevertheless, Annex IB explicitly exempts organisms obtained through this technique from the application of the legislation.
furthermore demand that these definitions should also be interpreted in a way that they are - apart from the technical difference with regard to cell fusion\textsuperscript{166} - consistent with each other.

Moreover, the subordinate position of the implementing measure with regard to the international agreement that it implements, demands that the former is interpreted in a way that it is consistent with the latter, and not \textit{vice versa}.

It should be noted here that the CPB itself on occasion foresees in a certain discretionary freedom for the parties in the implementation and transposition of the Protocol. Article 9 (2.(c)) in the context of the "Advance Informed Agreement" (A.I.A) procedure states that parties of import may communicate to the Party of export to proceed according to the domestic regulatory framework of the Party of import (instead of the procedure specified in article 10 of the CPB), however "The domestic regulatory framework referred to in in paragraph 2(c) above, shall be consistent with this Protocol."\textsuperscript{167}

In the case of Protocol party EU, this domestic regulatory framework for import of GMOs is embodied by Directive 2001/18/EC on the deliberate release, which incidentally also establishes the GMO definition that serves as the reference definition in EU GMO legislation. The above provision in the CPB therefore necessarily implies that Directive 2001/18/EC – and the provisions therein - should be consistent with the Protocol. Furthermore, the Protocol does not in any way state or suggest that - as an exception to the obligation of consistency – parties may establish scope definitions in their framework for the import of GMOs that divert from the scope definitions in the Protocol in a way that they are not consistent.

Moreover, as the Commission's phrasing "\textit{largely consistent}" in the abovementioned explanatory memorandum suggests an extensive compatibility between the two definitions, this a fortiori suggests that the essential, \textit{i.e.} constitutive elements in both definitions do not contradict each other.

It would also for this reason not be defendable to give a strictly technique-based interpretation to the terms "...altered in a way..." in the EU GMO definition, given that the CPB clearly states that both a new (novel) combination of genetic material and the use of a technique of genetic modification (modern biotechnology) constitute a GMO (LMO). The solely technique-based interpretation is not consistent with the text of the definition in the Protocol and would therefore infringe on the EU

\textsuperscript{166} \textit{cf. supra}, footnote 165
\textsuperscript{167} Article 9.3 CPB
legislator's intention to establish a coherent implementation of the provisions in the CPB and infringe on the EU's duty to respect its international obligations.

For those reasons, the terms "...altered in a way..." should, in accordance with the CPB, be interpreted as referring to both the use of a technique of genetic modification and the establishment of (a) new combination(s) of genetic material as a result thereof.

It should lastly be explained here why this thesis intentionally considers the requirement of "the establishment of (a) new combination(s) of genetic material in an organism" instead of the "presence of 'new' genetic material" in the organism.

While the GMO definition does refer to the introduction of nucleic acid molecules/heritable material in an organism in Annex 1A Part 1 (1) and (2), it is not entirely legally accurate and plausible to identify this element as a constitutive element in the GMO definition.

The criterion of "an alteration of genetic material" in article 2(2) does not necessarily imply that this genetic material contains 'new' DNA. Genetic material can also be altered through for instance a deletion or a mutation.

Moreover, the CPB in article 3(g) explicitly considers a novel combination of genetic material"as a constitutive element, and not the presence of 'new' introduced nucleic acid sequences.

**Article 2(2) and primary EU legislation: the precautionary principle?**

It should be noted here that the above interpretation of the terms "...altered in a way..." largely relies on the evaluation of the systemic coherence of article 2(2) of Directive 2001/18/EC with other provisions of secondary EU legislation.

As discussed in subchapter 2.1.7, secondary EU legislation has to conform with – and is therefore to be interpreted in a way that it is conform primary EU legislation.

The subordinate position of both Directive 2001/18/EC and the CPB vis à vis the EU constituting treaties - and the principles and provisions therein - namely demands that the provisions in the former documents are interpreted in a way that they conform with the latter.

The question therefore remains if -and if so- to what extent the above interpretation conforms with primary legislation.

It is not self-evident to identify potentially overriding principles or provisions of primary legislation.
Given the prominent position of the precautionary principle in EU environmental and GMO legislation, it will hereafter be evaluated if the above interpretation of the terms "...altered in a way..." could be affected by this principle of primary legislation.

Article 191 (2) TFEU states that EU policy on the environment "...shall be based on the precautionary principle...". The precautionary principle 168 furthermore has a very prominent position in the EU regulatory framework for GMOs. 169

While the principle itself remains undefined in the Treaty and in other EU legislation 170, the EU Commission has outlined its approach to using the principle and established guidelines on the principle's application in a communication dating from February 2000 171.

The Commission on page 13 considers: "The precautionary principle is relevant only in the event of a potential risk, even if this risk can not be fully demonstrated or quantified or its effects determined because of the insufficiency or inclusive nature of scientific data."

Application of the precautionary principle therefore presupposes an event of potential risk.

It should be noted here that the EU GMO definition itself in article 2(2) of Directive 2001/18/EC does not in any way refer to risk: it refers to novelty through alteration instead.

Notwithstanding the fact that the EU GMO legislation is aimed at controlling risks from – among others- the deliberate release of GMOs in the environment 172, the law does not in any way state or suggest that the term "GMO" or the use of a GM technique is defined as something inherently risky 173

In addition, the GMO regulatory framework prescribes authorisation procedures for GMOs. In the

168 The precautionary principle/approach finds its legal origin in Principle 15 of the UNCED Rio de Janeiro Declaration of 1992: "In order to protect the environment, the precautionary approach shall be widely applied by States according to their capabilities. Where there are threats of serious or irreversible damage, lack of full scientific certainty shall not be used as a reason for postponing cost-effective measures to prevent environmental degradation."
169 e.g. Recital 8 of Directive 2001/18/EC states: "The precautionary principle has been taken into account in the drafting of this Directive and must be taken into account when implementing it."; Article 1 of Directive 2001/18/EC states: 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, - placing on the market genetically modified organisms as or in products within the Community."
172 cf. Recital 5 of Directive 2001/18/EC
173 Additional support for this assumption can be found in the balanced regulatory approach for GMOs in the EU, which has taken the shape of authorisation procedures. If the term "GMO" itself were to refer to risk or danger, these organisms would simply be banned: quod non.
context of these procedures, a risk assessment has to be carried out in order to evaluate whether or not there is risk associated with the GMO.

In contrast with this last consideration, if the GMO definition itself were to refer to risk, *quod non*, this would imply that only risky GMOs would be subject to the authorisation procedures and the risk assessment requirement, and those GMOs that are not risky, would escape the scope of the law.

Application of the precautionary principle on the GMO definition would therefore result in a circular legal logic, which would be irreconcilable with the purpose of the GMO law.

It should lastly be stressed again that "risk" and "novelty" legally remain two very distinct concepts.

For these reasons, the precautionary principle is very unlikely to impinge on the above interpretation of the terms "*...altered in a way...*".

"*...that does not occur naturally...*" *quid?*

With regard to the question as to what constitutes an alteration “*...that does not occur naturally...*” in the light of the definition, the EU law remains silent.

It is however clear that, in the redaction of the GMO definition, the EU lawmaker intended to make the distinction between genetic alteration through the use of modification techniques and genetic alteration through natural processes. The latter kind of genetic alteration was not intended to be captured by the GMO law.

Article 2(2) of Directive 2001/18/EC states this very clearly: "*An organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally through mating and/or natural recombination.*"\(^{174}\)

\(^{174}\) It is sometimes suggested that the terms "*...that does not occur naturally...*" should be equated to "*...that is not possible to occur naturally..."*. Even though the Dutch version of article 2(2) of Directive 2001/18/EC mentions "*op een wijze welke van nature door voortplanting en/of natuurlijke recombinitie niet mogelijk is.*" (i.e. that is not possible in nature), there is probably no additional legal evidence in support of this premise. Moreover, the distinction appears to be of a theoretic nature, and is unlikely to affect the subsequent evaluation of the regulatory status of plants produced through NBTs.
Moreover, indent (1) and (3) of Annex IA Part 1 of the Directive reiterate this "requirement": "...in which they do not naturally occur..." (1) and "...that do not occur naturally..." (3).

This assumption is furthermore supported by the exception of "natural processes such as: conjugation, transduction, transformation..." in indent (2) of Annex IA Part 2.

As demonstrated above, the terms "...altered in a way..." should be equated to both the use of a technique of genetic modification and the establishment of (a) new combination(s) of genetic material. This necessarily implies that both the process/technique and the new combination(s) of genetic material do not "...occur naturally through mating and/or natural recombination."

Whether or not a process/technique and the new combination of genetic material do (not) occur naturally through mating and/or natural recombination, is therefore the decisive criterion with regard to what a genetic alteration is that would be captured by the law.

In addition, the Cartagena Protocol prescribes a similar requirement in its LMO definition. Article 3 (i) only considers techniques "...that overcome natural physiological reproductive or recombination barriers and that are not techniques used in traditional breeding and selection..." as techniques of "modern biotechnology".

Whereas this condition seemingly only relates to the application of techniques of "modern biotechnology", the phrasing of this provision necessarily also relates to the result, i.e. the new (novel) combination of genetic material obtained through the use of these techniques.

A natural physiological reproductive barrier is namely a barrier where the physiology of the individuals concerned would normally prevent exchange of genetic material. A natural reproductive barrier is one where various mechanisms, which could include, but are not limited to, physiological mechanisms, prevent exchange of genetic material.176

The above provision in the CPB necessarily implies that, if the use of "in vitro nucleic acid

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175 It is very unclear if - and if so - to what extent the three indents of Annex IA Part 1 set requirements. It could be argued that they are merely indicative and descriptive. Therefore, this systemic argument should be nuanced. Refer to subchapter 2.1.12.

"...or fusion of cells beyond the taxonomic family..." establishes a novel combination of genetic material that could also be established by the exchange of genetic material of individuals that are not imposed by a natural physiological reproductive or a natural reproductive barrier, these techniques cannot be considered techniques of "modern technology". The resulting organism can in that case not be an LMO.

It is clear that this provision in the CPB corresponds to the "...that does not occur naturally through mating..." requirement in Article 2(2) of Directive 2001/18/EC. In accordance with the former, the latter provision should therefore be given the same meaning.177

A natural recombination barrier, on the other hand, is one beyond which recombination would not be possible under normal conditions for an organism’s genetic system.178

The above provision in the CPB necessarily implies that, if the use of "in vitro nucleic acid techniques..." or "fusion of cells beyond the taxonomic family..." establishes a novel combination of genetic material that could also be established by a recombination that would be possible under normal conditions for the organism's genetic system, these techniques cannot be considered techniques of "modern technology". The resulting organism can in that case not be an LMO.

It is clear that this provision in the CPB corresponds to the "...that does not occur naturally through ...natural recombination..." requirement in Article 2(2) of Directive 2001/18/EC. In accordance with the former, the latter provision should therefore be given the same meaning.

The above legal considerations with regard to "...that does not occur naturally through...natural recombination..." necessarily affect not only the type, but also the amount of genetic change: In natural conditions and during conventional breeding, organisms are susceptible to many changes and variations (e.g. mutations, deletions, genome rearrangements, recombinations...) in their genome due to, for instance, spontaneous mutations. It is clear that these natural alterations are not intended to be targeted by the GMO law.179

However, there is no legally determined technical threshold that separates “amount of genetic change that occurs naturally” from “amount of genetic change that does not occur naturally”. Furthermore,

177 It is above demonstrated that the EU GMO definition has to comply with – and is to be interpreted in a way that it is consistent with the CPB.


179 This assumption is furthermore supported by the exception of "natural processes such as: conjugation, transduction, transformation..." in Annex IA Part 2 and the exemption of "mutagenesis" in Annex IB of Directive 2001/18/EC
such a threshold cannot in any way be derived from any part of the text\textsuperscript{180} nor the larger context of the law.

A considered alteration should therefore be subject to an ad hoc evaluation in the light of the "that does not occur naturally through mating and/or natural recombination." legal criterion.\textsuperscript{181}

\textbf{In conclusion:}

The combined (process + product) interpretation of the terms "...altered in a way..." seems to be the legally correct interpretation of the terms "...altered in a way..." in article 2(2) of Directive 2001/18/EC.

The mere use of one of the techniques of genetic modification (represented by indents (1), (2) and (3) of Annex IA Part 1) to "alter" an organism, therefore is not sufficient for it to legally establish a GMO. The abovementioned arguments demonstrate that the use of a technique of genetic modification must also establish (a) new combination(s) of genetic material in an organism before this can legally be considered a GMO.

This necessarily implies that both the process/technique and the new combination of genetic material do not "...occur naturally through mating and/or natural recombination."

The purely product-based interpretation is legally not defendable for the simple reason that such an interpretation is in straight contradiction with the text of the law and the initial intention of the legislator.

\textsuperscript{180} Neither Directive 2001/18/EC, nor the CPB contain such a specific technical provision.

\textsuperscript{181} In this context, it should be noted that the European Commission's Joint Research Center (JRC) in an authoritative report on NBTs concludes: "It can therefore be assumed that in the case of a plant genome, information on DNA sequence of at least 20 nucleotides is needed to be in a position to consider a certain DNA sequence as unique and to identify it as the result of a deliberate genetic modification technique."

Refer to: LUSSER et al., 2011, p. 165

The NTWG report in section 4.2 also puts forward a technical threshold of 20 nucleotide changes. This threshold is derived from statistical information on the likelihood of spontaneous DNA changes, given the plasticity of genomes in natural conditions.

While, as mentioned, this exact technical threshold of 20 nucleotides cannot in any way be derived from any part of the text nor the larger context of the law, it may correspond to the legal threshold of "...that does not occur naturally..." if this is the amount of genetic change needed to distinguish a genetic alteration through GM techniques from a genetic alteration through natural processes.
In absence of an exact technical threshold in the text and the context of the law with regard to the 
“...that does not occur naturally...” prescription, a considered alteration should on a case-by-case basis be evaluated in the light of this legal criterion.

2.1.9 "Heritable material”

Whereas Annex IA Part 1 (2) speaks of “the direct introduction into an organism of heritable material”, and Annex IA Part 1 (3) speaks of "...live cells with new combinations of heritable genetic material are formed through the fusion..." the question is whether this means that this introduced material must be inherited in the organism in question, or that it simply means that this introduced material must be capable of being inherited in the organism, regardless of actual inheritance of said material by the organism, in order for the technique of introduction to be considered a “technique of genetic modification” within the terms of the GMO definition.

First of all, it is clear that the terms “genetic material” and “heritable material” could be considered synonyms.\(^{183}\)

The wording of the terms “heritable ((genetic) material)” should first of all be evaluated in abstraction from the normative context.

The Oxford English Dictionary (OED)\(^{184}\) defines “heritable” as: “Capable of being inherited, inheritable”, and also as: “Naturally transmissible or transmitted from parent to offspring; hereditary”. The Merriam-Webster Dictionary (MWD)\(^{185}\) defines “heritable” as: “Capable of being inherited or of passing by inheritance”.

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182 The relevance of this discussion should be put in perspective. The discussion focusses on the meaning of the term "heritable material" and on the legal consequences tied to this meaning. It should however be noted that this term is situated in Annex IA Part 1 of Directive 2001/18/EC, which enumerates techniques that are to be considered "techniques of genetic modification" within the terms of the GMO definition. The list of techniques is however preceded by the words "inter alia". It could therefore be argued that the list is merely indicative and descriptive, and that it does not set legal requirements. Refer to subchapter 2.1.12.

183 http://www.merriam-webster.com/dictionary/heritable

184 http://www.oed.com/view/Entry/86228?redirectedFrom=heritable#eid

185 http://www.merriam-webster.com/dictionary/heritable
Given that the OED's second definition: “naturally...transmitted from parent to offspring” considers transmission instead of inheritance, it is of a too generic nature to be applied to the technical situation of the introduction of material in an organism: there is in casu no doubt about the fact that there is a transmission of material, but there is doubt about the inheritance of this material. Therefore this definition cannot be taken into consideration.

Considering the prevalence of the definition: “Capable of being inherited” in both the OED and the MWD, in a linguistic interpretation, the balance should be tipped in favour of the interpretation that this material must simply be capable of being inherited in order for a technique to be considered a “technique of genetic modification” within the terms of the GMO definition.

While the wording of the term “heritable (material)” is reasonably clear and therefore reasonably conclusive with regard to the legal interpretation, the question remains if there are arguments in the “Spirit” and the “General scheme”\footnote{Case C-26/62 Van Gend en Loos v Nederlandse Administratie der Belastingen} of the law that could override this literal interpretation and the adagio of in claris non fit interpretatio.

When these words are considered in coherence with the rest of the law and its larger context, it could be argued that this material \textit{must} be inherited, \textit{i.e.} must be incorporated and propagated in the organism, in order for a technique to establish a “technique of genetic modification” within the terms of the GMO definition.

One of the arguments supporting the premise that the genetic material must be inherited can be derived from Annex IA Part 1, which is of an indicative nature as to which techniques are techniques of genetic modification in the sense of the law:

Indent (1) of Annex IA Part 1 prescribes the 'requirement'\footnote{It is very unclear if - and if so - to what extent the three indents of Annex IA Part 1 set requirements. It could be argued that they are merely indicative and descriptive. Therefore, this systemic argument should again be nuanced. Refer to subchapter 2.1.12.}: ".. and their incorporation into a host organism in which they do not naturally occur but in which they are capable of continued propagation," which entails that modification of an organism through the recombinant DNA modification technique establishes a "technique of genetic modification" if the introduced genetic material is incorporated (inherited) and capable of continued propagation in the organism.
An interpretation of “heritable (genetic) material” in indent (2) and (3) that would imply that the introduced genetic material must merely be capable of being inherited would therefore be inconsistent with indent (1): introduced genetic material is only capable of “continued propagation” in the organism if it is actually incorporated (inherited) in said organism's genome.

It should in this context be noted that the techniques of genetic modification through recombinant DNA and through the use of the direct introduction/cell fusion are in practice the same with regard to their envisaged result: they all entail the introduction of genetic material in a host organism. They do however differ in their technical execution: modification by rDNA involves the use of a vector and modification by direct introduction/cell fusion does not.

It is in other words not sure if there currently is sufficient reason to differentiate in legal approach with regard to these techniques. Therefore, it could be argued that indents (1), (2) and (3) must be interpreted in a way that they are consistent with each other.

An important issue in this discussion revolves around the fact that the law mentions “the introduction of heritable material”, but does not appear to address any phenotypic changes and the heritability of these changes as a result of this introduction. Whereas some NBTs introduce genetic material in an organism that is not heritable by this organism, the genetic changes that are imparted by this introduction are heritable.

Additional legal clarification in this discussion is likely required.

When this discussion is evaluated in the light of the conclusions in subchapter 2.1.8 of this thesis, it appears that the supposed requirement of actual inheritance of the genetic material is in area of conflict with the necessary and pivotal requirement of the establishment of (a) new combination(s) of genetic material in the organism.

As mentioned, this requirement cannot be equated to the requirement of the presence of 'new' genetic material in the organism: a new combination of genetic material may also be established through a gene deletion or alteration. It is in the light of this constitutive requirement therefore not necessary that genetic material must be inherited in the organism's genome.

\[188\] In this context the history of genetic modification and the legislation should be taken into consideration: at the time of the redaction of the EU GMO definition in 1990, genetic modification through direct introduction and cell fusion was deemed to be the "newer form" of genetic modification, whereas genetic modification through rDNA techniques was already established in the 1970s. This could be a possible explanation as to why the EU legislator is less elaborate in his description of these techniques. There is however no (legal) evidence in support of this assumption.
In conclusion:

Whereas a literal interpretation of the term "heritable material" implies that this material must simply be able of being inherited, the general scheme of the law appears to suggest that this material must actually be inherited.

While some NBTs introduce genetic material in an organism that is not heritable by this organism, the genetic changes that are imparted by this introduction are heritable. Additional legal clarification is likely required.

When this discussion is evaluated in the light of the constitutive element of the establishment of (a) new combination(s) of genetic material (cf. Subchapter 2.1.8), it is apparent that genetic material must not necessarily be inherited: a new combination does not necessarily require the presence of 'new' genetic material in the organism's genome.

All in all, the relevance of this discussion should be put in perspective. The discussion focusses on the meaning of the term "heritable material" in Annex IA Part 1 of Directive 2001/18/EC, which enumerates techniques that are "inter alia" to be considered "techniques of genetic modification" within the terms of the GMO definition. It could be argued that the list of techniques in Annex IA Part 1 is merely indicative and descriptive, and that it does not set legal requirements.  

2.1.10 Is a GMO offspring a GMO?

Some of the transgenic construct-driven breeding techniques examined in this thesis involve an intermediate step in which the genetic material of an organism is altered, where after this organism is induced to reproduce. The offspring of this organism will not necessarily contain a genetic alteration.

189 For this reason, the subsequent checklist of constitutive elements that give rise to a GMO in chapter 3 will not refer to any requirement of heritability of introduced genetic material. This is however unlikely to affect the final conclusions with regard to the regulatory status of plants produced through the examined NBTs.

190 Reverse breeding and RdDm
Nor the text of the GMO law, nor its larger legal context (explicitly) refer to the offspring of a GMO. It is therefore pertinent to ask the question to what extent a resulting offspring organism should be qualified as a GMO.

First of all, it should be noted that the offspring of a GMO in itself is an organism, that has to be distinguished from its parent organism. Whether or not, and to what extent this organism is also a GMO, should therefore again be evaluated in the light of the GMO definition. It must in other words be evaluated if the genetic material in this organism "...has been altered in a way that does not occur naturally through mating and/or natural recombination."\(^{191}\)

Subchapter 2.1.8 has demonstrated that a legally correct interpretation of the terms "altered in a way" in the GMO definition implies that genetic material is "altered" if it has both undergone a technique of genetic modification and this has led to the establishment of (a) new combination(s) in said material.

The genetic material in the offspring organism should therefore again be evaluated in the light of these two base requirements.

With regard to the first base requirement of "the application of a technique of genetic modification", it should be noted that this notion does not refer to a result. It merely refers to a process of introduction of genetic material in an organism (by whatever GM technique).

It is in the light of this condition however not required that there is 'new' genetic material still present in the organism's genome: the genetic material in the organism must simply have undergone a process of introduction of genetic material (by whatever GM technique), regardless of actual presence or absence of this introduced genetic material in the resulting organism's genome.\(^{192}\)

As a parent/ancestor organism is a GMO, this per definition implies that its genetic material has undergone a technique of genetic modification. A GMO offspring will in all possible cases of reproduction (e.g. sexual, vegetative) end up containing 'modified' genetic material from its parent/ancestor organism.

Therefore, as long as an offspring organism contains genetic material derived from a genetically

\(^{191}\) Art. 2(2) of Directive 2001/18/EC

\(^{192}\) The NTWG report on page 8 states: All experts agreed that once it is established that the 'foreign' genetic material is no longer present in the resulting organism it is no longer considered a GMO. This is not legally accurate.
modified parent/ancestor, the base requirement of "the application of a technique of genetic modification" is met.

In a first provisional conclusion, an offspring organism of a GMO can only be a GMO if this organism at least contains genetic material that has undergone a technique or process of genetic modification. This requirement is met as soon, and as long as the offspring contains genetic material derived from its GMO parent/ancestor.

With regard to the second base requirement of "the establishment of (a) new combination(s) of genetic material", it should be noted that this notion does refer to a result. It refers to (a) new combination(s) of genetic material in the organism: 'new' genetic material is added to the genome, or the genome has been altered by a gene deletion or alteration.

As a parent/ancestor organism is a GMO, this per definition implies that its genetic material contains (a) new combination(s) of genetic material. A GMO offspring will in all possible cases of reproduction (i.e. sexual, vegetative) end up containing genetic material from its parent/ancestor organism. However, this genetic material will not always contain (a) new combination(s).

- In the case of vegetative reproduction, the entire parent organism's genome is inherited. Barring the case where the genetic alteration disappears over time in subsequent generations\(^{193}\), this implies that the offspring organism will always inherit (a) new combination(s) of genetic material from its parent organism. GMO offspring organisms obtained through vegetative reproduction are therefore always GMOs.

- In the case of sexual reproduction, only half of the parent organism's genome will be inherited by the organism. This implies that the offspring organism has a one in two chance to inherit (a) new combination(s) of genetic material from its parent. GMO offspring organisms obtained through vegetative reproduction are therefore not always GMOs. In every case, it will have to be evaluated if genetic material containing (a) new combination(s) of genetic material was inherited.\(^{194}\)

\(^{193}\) cf. the discussion on transient expression and presence of a genetic alteration.

\(^{194}\) In the case where the parent organism contains multiple alteration of genetic material, this evaluation becomes complicated. It must -among others- be evaluated if these alterations reside on the same, or a different locus in the
In a second conclusion, an offspring organism of a GMO is a GMO if this organism has inherited genetic material that contains (a) new combination(s) of genetic material: 'new' genetic material has been added to this inherited material, or this inherited material has been altered by a gene deletion or alteration.

In the case of sexual reproduction, it will have to be evaluated whether or not, and to what extent the inherited genetic material of the offspring organism contains (a) new combination(s) of genetic material.

In conclusion:

An offspring organism of a GMO is a GMO if this organism contains genetic material that has undergone a technique or process of genetic modification. This requirement is met as soon, and as long as the offspring contains genetic material derived from a GMO parent/ancestor.

In addition, the offspring organism of a GMO is only a GMO if this organism has inherited genetic material that contains (a) new combination(s): genetic material has been added to this inherited material, or this inherited material has been altered by a gene deletion or alteration.

2.1.11 Recombinant nucleic acid molecules

The term "recombinant nucleic acid molecules" is mentioned in Annex IA Part 2 and Annex IB of Directive 2001/18/EC. The techniques listed in these parts of Annex I are respectively excluded from

parent's genome.

195 The new combination must, in accordance with article 2(2) of Directive 2001/18/EC remain a new combination that "does not occur naturally through mating and/or natural recombination".

196 The authors of the authoritative IUCN explanatory guide on the Cartagena Protocol come to a similar conclusion with regard to the LMO definition: "The criterion that determines whether an organism is a LMO under the Terms of the Protocol is the application of an in vitro nucleic acid technique, or a cell fusion technique beyond the taxonomic family, to obtain an organism that contains a novel combination of genetic material. Any organism into which such a novel combination of genetic material is subsequently transferred, even if that transfer is achieved through traditional breeding and selection techniques, will also be a LMO under the terms of the Protocol." Subchapter 2.1.8 has demonstrated that the EU GMO definition is to be interpreted in a way that it is consistent with the LMO definition in the CPB.


the GMO definition and exempted from the directive, unless they involve the use of "...recombinant nucleic acid molecules..." or "...genetically modified organisms made by techniques/methods other than those excluded by Annex IB...genetically modified organisms other than those produced by one or more of the techniques/methods listed below...".

The question is what exactly constitutes a recombinant nucleic acid molecule in the sense of the law. 198

Whereas there is no doubt that it implies the formation of a new combination 199 of genetic material outside of the targeted organism’s cell, it is unsure what exactly constitutes this new combination. Does the replacement of just one nucleotide in a sequence entail a new combination in the sense of the law? Or does it take more than that?

While, as mentioned, the text of the GMO law does not provide a definition for the term "recombinant nucleic acid molecule", it does however implicitly touch on this concept in indent (1) of Annex IA Part 1 of Directive 2001/18/EC. This provision refers to “recombinant nucleic acid techniques” 200: these techniques are – according to the logic of the law – intended to alter an organism’s genetic material “in a way that does not occur naturally through mating and/or natural recombination”. 201 202

This provision suggests that a recombinant nucleic acid molecule is a molecule that is used to alter an organism's genetic material “in a way that does not occur naturally through mating and/or natural recombination".

It should be noted that the alteration of genetic material in an organism “in a way that does not occur naturally through mating and/or natural recombination" is only possible if the vector, i.e. carrier organism that is used to transfer the alteration-inducing genetic material itself contains

198 In a scientific context, there is a straightforward definition for this term; a recombinant nucleic acid molecule is namely a nucleic acid molecule that is composed of at least two parts that have a different origin. This thesis however will only look for legal arguments in order to find explanation for the unclarities in the EU GMO definition.
199 The term "recombinant" implies a recombination or new combination: it is a compound molecule.
200 “(1) Recombinant nucleic acid techniques involving the formation of new combinations of genetic material by the introduction 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”
201 Subchapter 2.1.8 has however demonstrated that the mere use of this technique is not a sufficient requirement to establish a GMO.
202 Moreover, indent (1) mentions "in which they do not naturally occur but in which they are capable of continued propagation."
genetic material that has been “altered in a way that does not occur naturally through mating and/or natural recombination”.\textsuperscript{203}

Therefore, the new combination of genetic material in the recombinant molecule should also be a combination “that does not occur naturally through mating and/or natural recombination”. A different interpretation would not be consistent with the general scheme – and would be illogical in the light of the law.

Furthermore, as mentioned in subchapter 2.1.8, the requirement "...that does not occur...through natural recombination." both considers the type, as well as the amount of genetic change.

However, there is no legally determined technical threshold that separates “amount of genetic change that occurs naturally” from “amount of genetic change that does occur naturally”. Furthermore, such a threshold cannot in any way be derived from any part of the text nor the larger context of the law.

A considered new combination should therefore be subject to an ad hoc evaluation in the light of the ...”that does not occur naturally through mating and/or natural recombination.” legal criterion.

In conclusion:

It appears that a recombinant nucleic acid molecule is established by a new combination of genetic material in a vector molecule outside of the targeted organism’s cell. This new combination is a combination that does not occur naturally through mating and/or natural recombination.

\textbf{2.1.12 "...inter alia..." and similarity}

Annex IA Part 1 of Directive 2001/18/EC states: "Techniques of genetic modification referred to in Article 2(2)(a) are inter alia:..." and subsequently enumerates three techniques that are to be considered "techniques of genetic modification".

\textsuperscript{203} A recombinant nucleic acid molecule is therefore necessarily a GMM in the light of the GMM definition as set out by Directive 2009/41/EC.
The question is to what extent other molecular techniques, that may or may not resemble the techniques explicitly listed, are also covered by this part of Annex IA.

Annex IA Part 2 of Directive 2001/18/EC states: "Techniques referred to in Article 2(2)(b) which are not considered to result in genetic modification, on condition that...:" and subsequently enumerates three techniques and processes that are not considered to result in "genetic modification". The question is to what extent other molecular techniques, that may or may not resemble the techniques explicitly listed, are also covered by this part of Annex IA.

Annex IB of Directive 2001/18/EC states: "Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that...:" and subsequently enumerates two techniques/methods of genetic modification that yield organisms to be exempted from the directive. The question is to what extent other molecular techniques/methods, that may or may not resemble the techniques/methods explicitly listed, are also covered by Annex IB.

As mentioned before, these three parts of Annex I of Directive 2001/18/EC originate in Directive 90/220/EC. The historic changes and amendments to this directive have never substantially affected Annex I. Moreover, the changes imparted by Directive 2001/18/EC were largely of an editorial nature (cf. supra). The text of the three parts of Annex I therefore nowadays still represents the legal conception of "genetic modification", as it was known in 1990.

The application of "genetic modification", and more specifically the NBTs, in practice in 2015 and in the following years raises questions as to how Annex I should be interpreted.

Again, first and foremost, the wording in this Annex should be evaluated.

Annex IA Part 1 contains the wording “inter alia”, which means “among other things”\(^{204}\). Therefore, the EU law suggests that genetic modification does not necessarily only happen through the techniques represented by indents (1), (2) and (3). The list of techniques of genetic modification in Annex IA Part 1 is in other words not exhaustive but

\(^{204}\) http://www.merriam-webster.com/dictionary/inter%20alia
of an indicative nature.

Both Annex IA Part 2 and Annex IB do not contain the wording "inter alia". While it would appear that the techniques/methods enumerated in these parts of Annex I are therefore the only techniques/methods excluded from the definition/exempted from the Directive, this does however not necessarily imply that these parts of the annex are strictly exhaustive and strictly not indicative. Annex IA Part 2 (2) namely mentions: "natural processes such as: conjugation, transduction, transformation,..." and therefore suggests that also other natural processes could be excluded from the scope of the definition. For that reason, at least indent (2) of Annex IA Part 2 is not exhaustive and of an indicative nature.

Moreover, as mentioned above, the European Court of Justice has in the past - albeit conditionally - accepted analogical application of written provisions of EU law to situations that are not expressis verbis covered by said provisions. The scope of Annex IA Part 2 and Annex IB may therefore be extended to other techniques that are not explicitly mentioned in these provisions. It will hereunder be evaluated if, and to what extent, Annex IA Part 2 and Annex IB could be applied by analogy to other techniques/processes that are not explicitly mentioned.

It is on the other hand also not legally plausible to depart from the text of the law in a way that the wording of the text is disregarded: Annex IA Part 1 in its header contains the wording "inter alia", and Annex IA Part 2 and Annex IB do not.

It is therefore preliminarily safe to conclude that Annex IA Part 2 and Annex IB are at least of a more exhaustive and less indicative nature than Annex IA Part 1.

Furthermore, it is apparent that Annex IA Part 2 and Annex IB primarily emphasise on techniques/methods rather than on the result of the application of the techniques/methods. This can be derived from the wording of these provisions: "Techniques referred to in Article 2(2)(b) which are not considered to result in genetic modification,..." and "Techniques/methods of genetic modification yielding organisms to be excluded". The exclusion from the definition and the exemption from the Directive therefore depend on the technique/method that is used.
The fact that a certain technique that is not mentioned in these provisions imparts a result that resembles the result imparted by one of the techniques explicitly mentioned, may therefore legally not be relevant: the process, rather than the result, appears to determine exclusion from the definition and exemption from the law.

Furthermore, some interpretative indications on Annex I can be found in the larger context of Directive 2001/18/EC.

Recital 17 in the preamble of Directive 2001/18/EC reads: "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."

Whereas this recital does not elaborate on Annex IA Part 1 for it only considers organisms to which the Directive does not apply, it does elaborate on the nature of Annex IA Part 2 and Annex IB.

Two important considerations can be derived from this recital:

*Primo*, recital 17 does not necessarily confirm the exclusive emphasis on the process. Whereas "which have conventionally been used in a number of applications and have a long safety record" appears to be related to "techniques", it both linguistically and substantively could also relate to the "organism" obtained through the techniques: the relative pronoun "which" may in this sentence both refer to "organisms obtained through techniques..." and "techniques".

This could affect the regulatory status of NBTs: While the application of some of the new techniques discussed in this thesis gives rise to an organism that is similar to the organism obtained through techniques enumerated in Annex IA Part 2 and Annex IB, it is not sure if this is an argument in support of the premise that they could be captured by these provisions. If the focus in this recital strictly lies on techniques, this argument may not be relevant: there only is a resemblance in the resulting

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205 Recital 17 in the French version of Directive 2001/18/EC however provides: "La présente directive ne devrait pas s'appliquer aux organismes obtenus au moyen de certaines techniques de modification génétique qui ont été traditionnellement utilisées pour diverses applications et dont la sécurité est avérée depuis longtemps." Linguistically, the term "utilisées" can only relate to "techniques de modification génétique", and not to "organismes". In addition, Recital 17 in the Spanish version of Directive 2001/18/EC provides: "La presente Directiva no debe aplicarse a los organismos obtenidos mediante determinadas técnicas de modificación genética que han venido siendo utilizadas convencionalmente...." "Utilizadas" can linguistically only refer to "técnicas de modificación genética".
organism but not necessarily in the technique used.

Furthermore, it is important to note that the law uses the pronoun "which" instead of "that". "Which" is of a more descriptive nature and "that" is of a more limiting nature. The use of the word "which" seems to suggest that it is not necessarily only organisms/techniques "which have conventionally been used in a number of applications and have a long safety record" that are covered by these parts of Annex I.

Secundo, the law considers a conventional use and a long-lasting safety record of organisms/techniques that are excluded from the definition/exempted from the Directive. The wording of recital 17 clearly supports this assumption.

The criterion of "a long safety record" is from a legal point of view not self-evident to evaluate. Moreover, from a scientific point of view this criterion is open to interpretation and debate: When can a technique/organism be considered "safe"? What is "a long safety record"?

As this thesis primarily focusses on legal arguments, this criterion and its application on NBTs will not be evaluated.

While the criterion of a "conventional use" is of a generic nature and therefore also open to interpretation and debate, it is more objectively evaluable.

Given the relatively new and young nature of most of the New Breeding Techniques and the (still) somewhat limited use, the application of this criterion on these techniques and their resulting organisms appears to be problematic.

Furthermore, with regard to Annex I, the Commission in the explanatory memorandum accompanying Directive 90/220/EC on page 34 states: "This Annex is intended to provide, through a periodical update, as a clarification of what techniques can make an organism genetically modified" within the meaning of this Directive. The techniques not covered are those that have long been used with crop plants and livestock with an excellent safety record."

First of all, the Commission confirms the assumption that Annex IA Part 1 is of an indicative nature. It is moreover interesting that the EU lawmaker never followed up on the intention to periodically

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update Annex IA (Part 1).

Whereas recital 17 still leaves room for interpretation with regard to what techniques/organisms are excluded/exempted, this consideration by the Commission is clearer and of a more specific nature.

The Commission clearly only considers the techniques and not the result of the application of the techniques. "The above text clearly supports this assumption.

Moreover, the Commission here uses the pronoun "that" instead of "which". It therefore suggests that only techniques "that have long been used with crop plants and livestock with an excellent safety record." are excluded/exempted.

Both the wording of Annex IA Part 2, Annex IB and this consideration by the Commission suggest that the process, rather than the result, determines exclusion from the definition.

Furthermore, strongly resembling the criteria of "conventional use" and "long safety record" in recital 17, the Commission here considers a "long-lasting use" and an "excellent safety record". The above conclusions mutatis mutandis apply.

It furthermore appears that in addition to "techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record." Annex IA Part 2 (2) and Annex IB (2) cover processes/techniques that do occur naturally through mating and/or natural recombination. The wording of these provisions clearly supports this assumption.

Lastly, it should be evaluated to what extent Annex IA Part 2 and Annex IB can be applied by analogy to techniques, more specifically NBTs, that are not explicitly covered.

As mentioned, the European Court of Justice has established its doctrine on analogical application of written provisions of EU law in its Krohn v Balm\textsuperscript{207} jurisprudence.

The Court prescribes two necessary requirements in order to apply the EU rule by analogy: the rule that would normally be applicable to a given situation 1) is very similar to the one that is sought to

\textsuperscript{207} Case C-165/84 Krohn v Balm (13-14)
be applied by analogy and 2) contains an omission that is incompatible with a general principle of Community law and which can be remedied by application by analogy of that other rule.

First of all, the rule "that would normally be applicable" to NBTs should be identified. It is very likely that this rule is Annex IA Part 1: most of the NBTs examined in this thesis make use of a technique of genetic modification listed in Annex IA Part 1. The NBTs that make use of a different – but resembling – technique may also be covered as this part of Annex I is of non-exhaustive and indicative nature. It may therefore also cover techniques that are not expressis verbis mentioned. Furthermore, there are no indications in "the spirit, the general scheme and the wording" of the law that further outline or limit the non-exhaustive and indicative nature of Annex IA Part 1.

It appears that the analogical application of Annex IA Part 2 and Annex IB to NBTs will be problematic in the light of the Krohn v Balm²⁰⁸ jurisprudence.

Annex IA Part 1 (the rule normally applicable) is not at all similar to Annex IA Part 2 and Annex IB (the rule that is sought to be applied by analogy). Whereas the application of Annex IA Part 1 entails inclusion in the GMO definition, the application of Annex IA Part 2 and Annex IB respectively entails exclusion from the GMO definition and exemption from the Directive.

It is not sure if Annex IA Part 1 (the rule normally applicable) furthermore contains an omission that is incompatible with a general principle of Community law and which can be remedied by application by analogy of Annex IA Part 2 and Annex IB (that other rule).

It should lastly be noted that both Annex IA Part 2 and Annex IB prescribe the condition “on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms made by techniques/methods other than those excluded by Annex IB / other than those produced by one or more of the techniques/methods listed below...”²⁰⁹.

In conclusion:

The extension of the application of Annex IA Part 1 to NBTs will in most cases not be problematic as this part of Annex I is of non-exhaustive and indicative nature. It may therefore also cover

²⁰⁸ Case C-165/84 Krohn v Balm (13-14)
²⁰⁹ cf. Subchapter 2.1.12
techniques that are not *expressis verbis* targeted.\textsuperscript{210}

While it is clear that the techniques and processes covered by this part of Annex I are techniques and processes that should be distinguished from natural techniques and processes\textsuperscript{211}, there are furthermore no indications in "the spirit, the general scheme and the wording"\textsuperscript{212} of the law that further outline or limit the non-exhaustive and indicative nature of Annex IA Part I.

As most of the NBTs examined in this thesis make use of a technique of genetic modification listed in the law or a technique similar to a technique of genetic modification listed in the law, they will most likely be captured by Annex IA Part I\textsuperscript{212}.

The extension of the application of Annex IA Part 2 and Annex IB to NBTs on the other hand, will in some cases be problematic.

These parts of Annex I are of a more exhaustive and less indicative nature than Annex IA Part 1. While it could be argued that they are not strictly exhaustive and not strictly not indicative, the scope of these provisions is undeniably outlined by a number of legal considerations:

- They appear to target techniques/processes rather than the result of the techniques/processes: the process, rather than the result, determines exclusion from the GMO definition and exemption from the law.

- The techniques/processes covered by these provisions are required to meet criteria of "a conventional use" and "a long safety record" or are processes that occur naturally.

- The techniques/processes covered by these provisions may not involve the use of recombinant DNA molecules.

Furthermore, the application of these provisions by analogy on NBTs is probably not possible in the

\textsuperscript{210} The abovementioned report by the NBT Platform appears to consider legal requirements with regard to the techniques enumerated in Annex IA Part 1. This thesis does not subscribe to such a restrictive interpretation of Annex IA Part 1 because it is in conflict with the wording "*inter alia*" and the indicative and non-exhaustive nature of this part of Annex I.

\textsuperscript{211} cf. Art. 2(2) "...that does not occur naturally through mating and/or natural recombination." and Annex IA Part 1 (1) "...in which they do not naturally occur..." and (3) "...by means of methods that do not naturally occur..." of Directive 2001/18/EC.

\textsuperscript{212} This does however not mean that they are necessarily captured by the GMO definition.
light of the European Court of Justice's jurisprudence.
3. The EU regulatory status of plants produced through NBTs

The conclusions in the above subchapters lead to the following checklist of legal requirements that constitute a GMO in the sense of Directive 2001/18/EC:

A GMO is:

- An organism, which is a biological entity capable of replication or of transferring genetic material,
- that is not a human being,
- of which the genetic material has undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination,
- of which the genetic material contains a new combination that does not occur naturally through mating and/or natural recombination,
- that is not captured by Annex IA Part 2 of Directive 2001/18/EC.

In addition, it should be evaluated if an organism is obtained through any of the techniques enumerated in Annex IB of Directive 2001/18/EC. Organisms obtained through these techniques are not subject to the requirements in the Directive.

Technique by technique will hereafter be evaluated in the light of the above checklist. It will be examined whether, and if so, to what extent, the plants produced through the NBTs are GMOs in the sense of Directive 2001/18/EC. It will also be evaluated if the plants produced through the NBTs are captured by the scope of the GMO legislation.

This thesis surveys and analyses the regulatory status of living plants produced through NBTs. These plants are per definition organisms, and not human beings. The first two criteria of the above checklist will therefore not be taken into consideration in the hereafter following legal analyses.

Some of the hereafter examined techniques give in a preparatory or intermediate phase rise to an

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213 This checklist may be supplemented with additional requirements, derived from the other ongoing discussions with regard to other unclarities in the EU GMO definition (e.g. "transient presence", "heritable material"). However, it is unlikely that these requirements will impinge on the subsequent final conclusions with regard to the regulatory status of plants produced through the evaluated NBTs.

214 RdDm and reverse breeding
organism, where after this organism is further developed in view of the establishment of a final organism.

For the sake of clarity, the regulatory status of both the "intermediate organism" and the "resulting organism" will be discussed separately.

In the case of grafting on GM rootstock, it will also be evaluated whether or not the fruits and seeds produced by the plant are GMOs, and if these fruits and seeds are captured by the GMO legislation.

### 3.1 Oligonucleotide Directed Mutagenesis (ODM)

Oligonucleotide Directed Mutagenesis (ODM) is a technique that induces a targeted mutation in the genetic material of a host organism.

A chemically synthesised oligonucleotide (nucleic acid molecule) is via direct introduction (by electroporation, polyethylene glycol-mediated transfection or natural uptake) paired with a piece of the DNA of a targeted organism. The oligonucleotide consists of nucleotides homologous to the organism's DNA, as well as one or more mismatching nucleotides. Subsequently, native repair enzymes in the plant restore the mismatching gene(s) using the corresponding nucleotide as a template. The repair results in a mutation, the reversal of an existing mutation or the induction of small deletions of the native DNA of the plant.

The oligonucleotide itself is not integrated in the plant's genome. It degrades in the cells.\(^{215}\)

### 3.1.1 Legal analysis

Has an organism produced through ODM undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?\(^ {216}\)

\(^{215}\) **LUSSER et al.**, p. 24; NTWG report, p. 11-12

\(^{216}\) The answer to this question could be affected by the discussion on whether or not the legal notion of a "technique of genetic modification" demands that a considered technique inserts genetic material that is heritable by the organism in order for this technique to be qualified as such.

This thesis rejects the argument that Annex IA Part 1 of Directive 2001/18/EC sets legal requirements, as the header of this Annex contains the words "inter alia". The "heritable material" discussion will therefore not be taken in consideration here.
Oligonucleotides are introduced by vector-less direct introduction, which is a GM technique captured by Annex IA Part 1 of Directive 2001/18/EC. This process does not occur naturally through mating and/or natural recombination.

**Does an organism produced through ODM contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination?**

The introduction of oligonucleotides establishes a new combination of genetic material: ODM results in a mutation, the reversal of an existing mutation or the induction of small deletions in the genetic material of the plant.

This new combination however will in most, if not all, cases be a new combination that **does** occur naturally through mating and/or natural recombination.

With regard to the type of alteration, it is clear that the mutations induced by ODM are a type of recombinations that do occur naturally, as mutations in nature are of a random nature and are in no way limited to any specific part of the genome.

Furthermore, with regard to the amount of alteration, given that ODM generally targets the alteration of just one or a few nucleotides, and given the plasticity of genomes in natural conditions, this alteration would not meet the "that does not occur naturally through mating and/or natural recombination" legal criterion.217

**Is ODM a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?**

A technique that involves the induction of a mutation of genetic material by the direct vector-less introduction of a synthesized oligonucleotide in an organism can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

**Is ODM a technique that is captured by Annex IB of Directive 2001/18/EC?**

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217 In this context, it should be noted again that the European Commission's Joint Research Center (JRC) has stated: "It can therefore be assumed that in the case of a plant genome, information on DNA sequence of at least 20 nucleotides is needed to be in a position to consider a certain DNA sequence as unique and to identify it as the result of a deliberate genetic modification technique."

Genetic alterations of under 20 nucleotides therefore probably escape the scope of the GMO definition: the definition only targets results that **can** be distinguished from naturally occurring results.

Refer to: LUSSEr et al., 2011, p. 165
A technique that involves the induction of a mutation by the direct vector-less introduction of a synthesized oligonucleotide in an organism may be captured by indent (1) of Annex IB of the Directive: ODM is a form of mutagenesis\(^{218}\).

ODM is however only captured by indent (1) of Annex IB on the condition that it does not involve the use of recombinant nucleic acid molecules or genetically modified organisms.

ODM will in most cases not involve the use of recombinant nucleic acid molecules. While it is clear that an oligonucleotide is a nucleic acid molecule, this can only be considered a recombinant nucleic acid molecule if it is constituted by the formation of a new combination of genetic material "...that does not occur naturally..."\(^{219}\). Oligonucleotides generally comprehend a very limited amount of nucleotide alterations. Oligonucleotides are therefore no recombinant DNA molecules.

**3.2 Zinc Finger Nuclease Technology (ZFN)\(^{220}\)**

*Zinc Finger Nuclease Technology (ZFN) is a molecular technique that allows the introduction of genetic alterations at a predetermined location in the genetic material of a host organism.*

A Zinc Finger Nuclease is a synthesised compound protein, consisting of a zinc finger\(^{221}\) based DNA binding module linked to a DNA cutting module. The nuclease is introduced to the cell by recombinant techniques or vector-less introduction.

When two ZFNs are bound to a specific DNA site in a targeted organism, they function in a scissor-like fashion: They each attach to the opposite native DNA strands, cleaving both strands which results in a double-strand break (DSB).

Three different forms of ZFN Technology have been developed:

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\(^{218}\) "Mutagenesis" refers to both a natural process and a manmade technique. In nature, organisms are susceptible to mutations in their genome due to for instance exposure to ionizing radiation. The manmade technique involves the deliberate use of a so-called mutagens: organisms are treated with a chemical agent or exposed to ionizing radiation and this induces random mutations in the genome.

\(^{219}\) As demonstrated in subchapter 2.1.11, this notion refers to the formation of a new combination genetic material "...that does not occur naturally..." outside of the targeted organism.

\(^{220}\) As discussed before, Zinc Finger Nuclease (ZFN) is a form of Site Directed Nuclease (SDN). The subsequent legal assessment with regard to the plants produced through ZFN mutatis mutandis applies to plants produced through other forms of SDN, such as TALEN, CRISPR and Meganucleases.

\(^{221}\) See: www.zincfingers.org
– **ZFN-1 Technology**: Native repair enzymes in the plant reattach the loose ends through non-homologous end-joining, resulting in a site-specific random mutation where the DSB was. Possible mutations are changes of a single/few nucleotides, short deletions and insertions.

– **ZFN-2 Technology**: Together with the ZFN, a repair template module in the form of an oligonucleotide homologous to the host's targeted DNA is introduced to the organism. The template indicates the desired alteration(s). Based on this template, native repair enzymes restore the double-strand break, generally resulting in a site-specific mutation or small insertions.

– **ZFN-3 Technology**: Through the use of homologous recombination the double-strand break is filled in with a piece of DNA (trans- or cisgene) to the organism. ZFN-3 is generally used to insert complete genes in the host organism's genome.222

### 3.2.1 Legal analysis

**Has an organism produced through ZFN undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?** 223

Zinc finger nucleases are introduced by recombinant DNA techniques or by vector-less direct introduction, which are GM techniques captured by Annex IA Part 1 of Directive 2001/18/EC. These processes do not occur naturally through mating and/or natural recombination.

**Does an organism produced through ZFN contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination?**

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222 LUSSER et al., p. 23; NTWG report, p. 14-16
223 This assumption could again be affected by the discussion on whether or not the legal notion of a "technique of genetic modification" demands that a considered technique inserts genetic material that is heritable by the organism in order for this technique to be qualified as such.
This thesis rejects the argument that Annex IA Part 1 sets legal requirements, as the header of this Annex contains the words "inter alia". The "heritable material" discussion will therefore not be taken in consideration here.
ZF-1, ZFN-2 and ZFN-3 all establish a new combination of genetic material: they result in a mutation, the reversal of an existing mutation, the deletion or addition of genetic material in the targeted plant's genome.

In the case of ZFN-1 and ZFN-2, this new combination however will in most, if not all cases be a new combination that does occur naturally through mating and/or natural recombination. With regard to the type of alteration, it is clear that the mutations induced by ZFN-1 and ZFN-2 are a type of mutations that do occur naturally, as mutations in nature are of a random nature and are in no way limited to any specific part of the genome. Furthermore, with regard to the amount of alteration: ZFN-1 and ZFN-2 generally target the alteration of just one or a few nucleotides. Given the plasticity of genomes in natural conditions, this alteration does not meet the "...that does not occur naturally through mating and/or natural recombination" legal criterion.

In the case of ZFN-3, the new combination however can be a new combination that does not occur naturally through mating and/or natural recombination. ZFN-3 namely establishes a new combination by the insertion of genetic material in the targeted organism's genome. With regard to this type of alteration, it appears that the introduction is used to overcome natural recombination and/or mating possibilities in the case where ZFN-3 is used to introduce transgenes, i.e. genetic material derived from a sexually non-compatible species in the targeted organism. This targeted organism therefore would be captured by the scope of the GMO definition. In the case where ZFN-3 is used to introduce cisgenes, i.e. genetic material derived from a sexually compatible species, the targeted organism will contain a new combination of genetic material that does occur naturally. This targeted organism therefore would escape the scope of the GMO definition.

**Is ZFN a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?**

A technique that involves the induction of a mutation (ZFN-1 and ZFN-2) or the introduction of genetic material (ZFN-3) by recombinant techniques or by direct vector-less introduction of a zinc finger nuclease in an organism can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

**Is ZFN a technique that is captured by Annex IB of Directive 2001/18/EC?**
A technique that involves the induction of a mutation by recombinant techniques or by the direct vector-less introduction of a synthesized nuclease in an organism may be captured by indent (1) of Annex IB of Directive 2001/18/EC: ZFN-1 and ZFN-2 are forms of mutagenesis.

ZFN-3 is not captured by Annex IB. As this technique involves the introduction of genetic material in a targeted organism's genome, it can clearly be distinguished from the techniques and processes enumerated in this part of Annex I.

ZFN-1 and ZFN-2 are however only captured by indent (1) of Annex IB on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms.

In the case where the ZFN construct is delivered in the organism by recombinant techniques, ZFN-1 and ZFN-2 necessarily make use of a recombinant nucleic acid molecule. These techniques can in that case not be captured by indent (1) of Annex IB.

In the case where the ZFN construct is delivered in the organism by direct introduction, they do not make use of a recombinant nucleic acid molecule.

In that case ZFN-1 and ZFN-2 could be captured by indent (1) of Annex IB.

3.3 Reverse breeding

*Reverse breeding is a multi-step modern breeding process where a genetic modification takes place in an intermediate phase.*

*A diploid heterozygous 'elite' starting plant is selected for its desired trait. Through gene-silencing, which involves a technique of genetic modification, the meiotic recombination capacity of this plant is suppressed.*

*Hereafter, the altered elite plant is induced to form haploid microspores in its flowers. These microspores are captured and then recombined through the use of Double Haploid Technology (DH) to form double haploids. This constitutes so-called homozygous 'parent' cells.*

*Subsequently, the double haploids that contain the genetic alteration are discarded. The double*
haploids that do not contain the alteration are used to reconstitute the elite starting plant. 224

3.3.1 Legal analysis

Has an organism produced through reverse breeding undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?

The gene silence in the intermediate organism is accomplished through the use of recombinant DNA techniques or by vector-less direct introduction, which are GM techniques captured by Annex IA Part 1 of Directive 2001/18/EC. These processes do not occur naturally through mating and/or natural recombination.

The resulting organism contains genetic material derived from its parent, which has undergone a technique of genetic modification, and therefore meets this requirement as well.

Does an intermediate organism produced through reverse breeding contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination? Does a resulting organism produced through reverse breeding contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination?

Reverse breeding establishes a new combination of genetic material in the intermediate organism: it results in a gene silence. This new combination does not occur naturally through mating and/or natural recombination.

In the final organism however, reverse breeding does not establish a new combination of genetic material: there is no genetic change present in this organism's genome.

Is reverse breeding a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?

A multi-step technique that involves the gene-silence of the meiotic recombination ability of an organism, the formation of double haploids and lastly the combination of double haploids to

224 LUSSER et al., p. 26; NTWG report, p. 36-37
reconstitute an alteration-free elite starting plant, can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

**Is reverse breeding a technique that is captured by Annex IB of Directive 2001/18/EC?**

A multi-step technique that involves the gene-silence of the meiotic recombination ability of an organism, the formation of double haploids and lastly the combination of double haploids to reconstitute an alteration-free elite starting plant, can clearly be distinguished from the techniques and processes enumerated in Annex IB of the Directive.

**3.4 RNA-dependent DNA methylation (RdDm)**

RNA-dependent DNA methylation (RdDm) is a technique that causes an epigenetic alteration\(^\text{225}\) of a resulting organism's heritable material through the use of the methylation of specific DNA sequences. The process of methylation involves the attachment of methyl groups to the targeted DNA sequence induced by the insertion of a DNA or RNA construct. The methylation results in the suppression of the expression of the targeted gene(s) in this intermediate organism (gene silence). The gene silence by methylation can hereafter be inherited through some generations of 'resulting organisms', but will eventually disappear, restoring the initial expression level of the gene.

Two\(^\text{226}\) different scenarios of RdDm in plants can be envisaged:

- **RdDm involves the insertion of genetic material, resulting in a new combination of genetic material in the intermediate organism. Both this inserted genetic material and the induced methylation are inherited by the subsequent generations of 'resulting organisms'.** (scenario 1)

- **RdDm involves the insertion of genetic material, resulting in a new combination of genetic material, without changing the nucleotide sequence itself, that may or may not be heritable by next generations.**

\(^\text{225}\) i.e. an alteration of specific DNA sequences, without changing the nucleotide sequence itself, that may or may not be heritable by next generations.

\(^\text{226}\) The NTWG report considers a third scenario, in which 'foreign' genetic material is inserted in the intermediate organism, but that is not capable of continued propagation. This thesis does not consider that possibility, as the above checklist of constitutive elements makes no referral to "continued propagation".

http://learn.genetics.utah.edu/content/epigenetics/
material in the intermediate organism. While the inserted genetic material is not inherited by
the subsequent generations, the gene-silence by methylation is passed on, but will eventually
fade. (scenario 2)\textsuperscript{227}

3.4.1 Legal analysis

Has an organism produced through RdDm undergone a process/technique of genetic
modification that does not occur naturally through mating and/or natural recombination?

The gene silence in the intermediate organism is accomplished through the use of a recombinant DNA
technique, which is a GM technique captured by Annex IA Part 1 of Directive 2001/18/EC. This
process does not occur naturally through mating and/or natural recombination.
The resulting offspring organism(s) contain(s) genetic material derived from its ancestor, which has
undergone a technique of genetic modification, and therefore meets this requirement as well.

Does an intermediate organism produced through RdDm contain a new combination of genetic
material that does not occur naturally through mating and/or natural recombination?

In both scenario 1 and 2, RdDm establishes a new combination of genetic material in the intermediate
organism: it results in the addition of genetic material in this organism's genome. This new
combination does not occur naturally through mating and/or natural recombination.

In scenario 1, RdDm establishes a new combination of genetic material in the resulting organism(s):
these organisms contain 'new' genetic material. This new combination does not occur naturally
through mating and/or natural recombination.

In scenario 2, RdDm does not establish a new combination of genetic material in the resulting
organism(s): the addition of methyl groups to the genetic material of the plant cannot be considered

\textsuperscript{227} LUSER \textit{et al.}, p. 25; NTWG report, p. 32
a “genetic alteration” in the sense of article 2(2) of Directive 2001/18/EC.\textsuperscript{228}

The resulting offspring organism(s) otherwise remain(s) free of any addition, deletion or mutation of genetic material. \textsuperscript{229}

**Is RdDm a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?**

A technique that causes an epigenetic alteration through the methylation of a specific DNA sequence in a targeted organism can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

**Is RdDm a technique that is captured by Annex IB of Directive 2001/18/EC?**

A technique that causes an epigenetic alteration through the methylation of a specific DNA sequence in a targeted organism can clearly be distinguished from the techniques and processes enumerated in Annex IB of the Directive.

**3.5 Agro-infiltration\textsuperscript{230}**

*Agro-infiltration involves the direct injection with a needleless syringe of an agrobacterium into plant leaves. The agrobacterium contains genetic material corresponding to a desired trait to be (over)expressed in the plant.*

*The introduced genetic material is generally not integrated in the cell's genome, but results in a local and transient (over)expression of a targeted gene or gene sequence. Integration of the introduced genetic material in the cell's genome is a rare event.*\textsuperscript{231}

\textsuperscript{228} cf. The NTWG report (not public) on page 34: "All experts also agree that the new methylation itself is not regulated by the Directives since methylation of nucleotides is not considered as an alteration of the genetic material in the sense of the Directives."

\textsuperscript{229} In addition, even in the case where it would be argued that the methylation should be considered a new combination of genetic material in the sense of the Directive, *quod non*, it should be noted that this would be a new combination that does occur naturally through mating and/or natural recombination: methylation of DNA is the result of a naturally occurring process.

\textsuperscript{230} Only the regulatory status of plants produced through Agro-infiltration *sensu stricto* will be evaluated here. To distinguish from "floral dip", whereby flowers or inflorescences are agro-infiltrated.

\textsuperscript{231} LUSSER *et al.*, p. 26; NTWG report, p. 28-29
3.5.1 Legal analysis

Has an organism produced through agro-infiltration undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?

Agro-infiltration involves the use of a recombinant DNA technique, which is a GM technique captured by Annex IA Part 1 of Directive 2001/18/EC. This process does not occur naturally through mating and/or natural recombination.

Does an organism produced through agro-infiltration contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination?

Agro-infiltration does not establish a new combination of genetic material in the organism. The introduction of genetic material results in local and transient phenotypic effects, but does not alter the genetic material itself.

In the rare case where the introduced genetic material is stably integrated in the organism's genome, agro-infiltration does establish a new combination of genetic material in the organism that does not occur naturally through mating and/or natural recombination.

Is agro-infiltration a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?

A technique that causes local and transient phenotypic effects in the form of the overexpression of (a) targeted gene(s) through the use of a recombinant DNA technique can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

Is agro-infiltration a technique that is captured by Annex IB of Directive 2001/18/EC?

A technique that causes local and transient phenotypic effects in the form of the overexpression of (a) targeted gene(s) through the use of a recombinant DNA technique can clearly be distinguished from the techniques and processes enumerated in Annex IB of the Directive.
3.6 Cisgenesis\textsuperscript{232}

Cisgenesis is a term used to describe the genetic alteration of a target organism by means of the insertion of genetic material derived from a sexually compatible organism. The introduction of so-called cisgenes is generally\textsuperscript{233} achieved through the use of recombinant DNA techniques, vector-less direct introduction or cell fusion.

The term "an organism produced through cisgenesis" will here be used to refer to an organism in which only genetic material derived from a sexually compatible organism is inserted, that is hereafter under the control of their natural gene expression signals in their natural orientation.\textsuperscript{234}

3.6.1 Legal analysis

Has an organism produced through cisgenesis undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?

Cisgenes are inserted by recombinant DNA techniques, direct vector-less introduction or cell fusion, which are GM techniques captured by Annex IA Part 1 Directive 2001/18/EC. These processes do not occur naturally through mating and/or natural recombination.

Does an organism produced through cisgenesis contain a new combination of genetic material

\textsuperscript{232} It should be noted here that cisgenesis is not necessarily a technique as such. "Cisgenesis" also refers to a set of techniques, or the result of a set of techniques that involve the transfer of genetic material derived from a sexually compatible organism to the targeted organism's genome. e.g. ZFN-3 and other forms of Side Directed Nuclease (SDN) can be used to insert cisgenes in a targeted organism: refer to the evaluation of the regulatory status of plants produced through ZFN-3 in subchapter 3.2.

\textsuperscript{233} cf. footnote 233

\textsuperscript{234} To distinguish from a so-called "cisgenic" organism that also contains transgene marker genes, transgene expression regulators or t-DNA borders (in the case where cisgenes are inserted by recombinant DNA techniques). This organism is in other words completely transgene-free.

\textsuperscript{235} LUSSER \textit{et al.}, p. 24; NTWG report, p. 21-22
that does not occur naturally through mating and/or natural recombination?

The insertion of cisgenes establishes a new combination of genetic material: cisgenesis results in the addition of genetic material to the genome of the targeted organism.

This new combination is however a new combination of genetic material that does occur naturally through mating and/or natural recombination.

Cisgenesis namely establishes a genetic result that can be obtained through conventional breeding/crossing, i.e. that does occur naturally through mating and/or natural recombination.

Is cisgenesis a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?

A technique that inserts genetic material derived from a sexually compatible organism in a targeted organism, can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

Is cisgenesis a technique that is captured by Annex IB of Directive 2001/18/EC?

A technique that inserts genetic material derived from a sexually compatible organism in a targeted organism, can clearly be distinguished from the techniques and processes enumerated in Annex IB of the Directive.

3.7 Grafting on GM rootstock

Grafting on GM rootstock involves the attachment of the scion of a plant to the rootstock of a genetically modified plant.

The attachment of a non-GM scion to a GM rootstock has no effect on the genetic material of the stems, leaves, flowers and fruits of the resulting chimeric organism.\textsuperscript{236}

\textsuperscript{236} LUSSER et al., p. 25; NTWG report, p. 25-26
3.7.1 Legal analysis

Has an organism produced through grafting on GM rootstock undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?

Have the from the organism derived fruits and seeds undergone a process/technique of genetic modification that does not occur naturally through mating and/or natural recombination?

The rootstock of the organism is genetically modified. This necessarily implies that the organism has undergone a technique of genetic modification. This process does not occur naturally through mating and/or natural recombination.

The from the plant derived fruits and seeds do not meet this requirement. The chimeric nature of the parent plant demands that the genetic material of the scion is distinguished from the genetic material of the rootstock of the parent organism.

The fruits and seeds are namely only the product of the scion of the plant; the genetic material of the plant's rootstock is not passed on.

The scion has not undergone a technique of genetic modification. Therefore, the fruits and seeds produced by this scion do not meet this requirement either.

In addition, the technique of grafting itself can arguably be qualified as a technique captured by Annex IA Part 1 of Directive 2001/18/EC for the simple reason that it is not a molecular technique.

Does an organism produced through grafting on GM rootstock contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination?

Do the from the organism derived fruits and seeds contain a new combination of genetic material that does not occur naturally through mating and/or natural recombination?

The rootstock of the organism is a GMO. This per definition implies that the whole organism contains a new combination of genetic material that does not occur naturally through mating and/or natural recombination.

The from the organism derived fruits and seeds do not contain any genetic alteration. Therefore, they
do not contain a new combination of genetic material whatsoever.

**Is grafting on GM rootstock a technique that is not captured by Annex IA Part 2 of Directive 2001/18/EC?**

The alteration of the genetic material of a plant through GM techniques and the subsequent attachment via grafting of this plant's rootstock to the unaltered scion of another plant are both techniques that can clearly be distinguished from the techniques and processes enumerated in Annex IA Part 2 of the Directive.

**Is grafting on GM rootstock a technique that is captured by Annex IB of Directive 2001/18/EC?**

The alteration of the genetic material of a plant through GM techniques and the subsequent attachment via grafting of this plant's rootstock to the unaltered scion of another plant are both techniques that can clearly be distinguished from the techniques and processes enumerated in Annex IB of the Directive.

### 3.8 Overview

<table>
<thead>
<tr>
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<th>Produces an intermediate organism captured by the scope of Directive 2001/18/EC?</th>
<th>Produces a plant that is a GMO?</th>
<th>Produces a plant captured by the scope of Directive 2001/18/EC?</th>
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<tbody>
<tr>
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<td>Grafting on GM</td>
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</table>
The chimeric plant is in this overview referred to as the intermediate organism, the from the plant derived fruit(s) and seed(s) is/are referred to as the (resulting) plant(s).
4. Concluding remarks

4.1 De lege lata

The EU regulatory framework for GMOs is in literature sometimes referred to as a "process-based" regulation: the mere use of a technique of genetic modification to produce an organism, supposedly suffices for this organism to be qualified as a "GMO" and to be captured by the scope of the law.

However, it appears that this relatively widespread assumption (and in some cases - critique) is not entirely warranted.

A close reading and interpretation of the text of the EU GMO definition, as set out by article 2(2) of Directive 2001/18/EC, based on by the European Court of Justice established interpretative criteria, leads to the conclusion that said definition also refers to the outcome of the process or technique applied. The application of a technique of genetic modification must namely also establish a new combination of genetic material that does not occur naturally in an organism, in order for this organism to be qualified as a GMO.

This interpretation relies on the consideration that article 2(2) is to be interpreted in a way that it is consistent with not only other provisions in the EU GMO legislation, but also with the LMO definition, as set out by article 3 (g), (h) and (i) of the Cartagena Protocol on Biosafety.

As a result, it appears that several New Breeding Techniques do not produce a plant that is captured by the scope of the current EU GMO legislation.

This conclusion however, comes as no surprise. A number of legal arguments in the text and in the context of the EU GMO law clearly suggest that the essence of the term “GMO” lies in the distinction

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that can be made between a modified, *i.e.* manufactured or manmade organism and an organism that occurs naturally.

As most of the NBTs evaluated give rise to an organism that cannot be distinguished from a naturally occurring organism, but merely mimic a result that occurs in nature, this resulting organism is not captured by the scope of the EU GMO law.

Furthermore, this conclusion is also in line with the general purpose of, and the underlying legislative motives that gave shape to the EU GMO law.

The EU legislator has set up a harmonized regulatory framework in the form of authorisation procedures that prescribe an environmental risk assessment that aims to identify and evaluate whether GMOs pose a risk when released in the environment.

Whether or not an organism is safe, is to be determined on the basis of the evaluation of the traits and characteristics of this organism, and the effects of these traits and characteristics on human and animal health and the environment. A safety assessment in other words aims to evaluate the product, and not the process by which this product is made.

In contrast, the strictly process-based interpretation of the EU GMO definition could lead to legal results whereby a “GM produced” plant that is indistinguishable from a naturally occurring plant would be captured by the law and the requirement of an environmental risk assessment.

In these particular cases, a process-based interpretation would render the pivotal legal requirement of an environmental risk assessment – and by extension, the whole GMO law - not only backwards, but also meaningless: the safety of a naturally occurring plant is namely not evaluated, so *why* should the safety of the exact same plant, but that was produced by a GM technique, be evaluated? Furthermore, considering the fact that a safety assessment only considers the product, and not the process by which this product is made, *how* can the safety of a plant, that has no characteristics nor traits that set it apart from a naturally occurring plant, be assessed?

Lastly, notwithstanding the fact that this thesis comes to a conclusion with regard to what *in essence* constitutes a GMO in the sense of the EU GMO law, there still remains a considerable amount of legal ambivalence linked to the GMO definition, and its application on organisms obtained through the most modern, and in the future to come new molecular techniques.

The in this thesis highlighted and briefly evaluated questions with regard to "heritable material", "transient presence" and “*inter alia*” reflect just a few of the other discussions linked to the regulatory status of NBTs that may be served with additional legal clarification.
The introduction to this thesis considered that law not seldom struggles to keep up with the rapid pace of scientific advances and developments in a technological society.

It is often not self-evident for lawmakers to foresee and anticipate future scientific developments in a way that not only minimises the potential risks and maximises the potential benefits that come with new techniques, but also in a way that does not obstruct the future development of potentially beneficial techniques.

The EU regulatory framework for modern biotechnology is a framework that is clearly marked by this underlying regulatory challenge and the delicate balancing act that comes with it.

More specifically, this regulatory challenge strongly reflects in the definition of the key scope term “GMO”.

In 1990, the EU lawmaker attempted to foresee and anticipate future scientific developments in the field of modern biotechnology by redacting a GMO definition of which the open character (cf. “inter alia”) was intended to capture not only organisms produced by existing techniques, but also to capture organisms produced by future techniques of modern biotechnology.

As mentioned before in this thesis, this “inter alia” legislative approach, and the large amount of room for legal interpretation that it entails, comes with the benefit that it allows a flexible and somewhat evolutive interpretation and application of the law.

This high flexibility of the law however comes at the cost of clarity and legal certainty.

In recent years, it has gotten increasingly more challenging to determine whether or not organisms obtained through new techniques of modern biotechnology are subject to the requirements in the GMO law.

More specifically, the debate with regard to the regulatory status of the organisms produced through New Breeding Techniques has been going on for many years now.

In this context, it should be noted that the EU Commission’s own “New Techniques Working Group”, which was in 2008 charged with the task to discuss and settle the legal questions, did not manage to reach unisonous conclusions with regard to a considerable amount of identified legal ambiguities.
Whereas - in general - all legal provisions and principles are subject to, and are served with a healthy amount of interpretative debate, the question should be asked whether or not the regulatory status of organisms obtained through New Breeding Techniques is subject to more debate than necessary.

This question could be answered affirmatively. While it is only normal that law struggles to keep up with the searing pace of technological advances and developments, it could be argued that it has started to fall too far behind.

Legal subjects involved in the research and development of New Breeding Techniques today identify the uncertainty with regard to the regulatory status, and the herewith closely connected uncertainty with regard to the potential level of regulatory requirements and legal costs, as major constraints for the development of the new techniques.\footnote{239}{Lusser et al., p. 49}

In other words, the absence of substantial changes to the GMO definition since the initial redaction, and the resulting questions with regard to the application of the definition on organisms produced through NBTs, appear to pose a threat to innovation.

The lingering debate with regard to the application of the GMO definition on organisms produced through NBTs, and the resulting excessive amount of legal uncertainty imposed on the legal subjects involved in the research and development of these techniques, may indicate that the EU GMO definition is due for an editorial update.

The question then remains how the GMO definition could be updated.

Two different legislative approaches can be envisaged.

The EU Commission and lawmaker may opt to maintain the established “inter alia” approach, and updates the lists of techniques that are included and excluded within the terms of the definition, and updates the list of techniques that lead to exemption from the scope of the GMO law in function of contemporary scientific knowledge and insights in molecular techniques.

In 1988, the EU Commission considered the following with regard to Annex IA Part 1 of Directive 2001/18/EC\footnote{240}{COM(88)6397, dating 24 May 1988.}: “This Annex is intended to provide, through a periodical update, as a clarification of
what techniques can make an organism genetically modified"within the meaning of this Directive."
As the discussions with regard to the regulatory status of organisms produced NBTs are to some extent caused by the inactivity of the EU Commission and lawmaker, maybe it is now time to carry out that periodical update?

The EU Commission and lawmaker may on the other hand also opt to completely reorient and restructure the GMO definition and the regulatory approach for GMOs in general.
The EU lawmaker may want to seize the opportunity to reconsider the current approach and to go back to the essence of why all new technologies in general are, and should be regulated: to legally ensure the safety of their products.
Twenty-seven years ago, the EU commission considered the following with regard to the new GMO law: 241
The present approach, which focusses on the new techniques of genetic engineering, is the first and most urgent step in the regulatory process; however, this will not impede evolution towards a more organism-related approach."
As concerns with regard to the safety of the products obtained through new techniques of modern biotechnology rightfully reflect the essence of why this field is regulated, maybe it is now time for that more product-related approach?

While both the above approaches may prove to have benefits as well as pitfalls, it appears that they will both require the additional clarification of a number of legal concepts.
One of those concepts is the criterion of the alteration “…that does not occur naturally…”
It appears that some of the newest, most modern techniques of modern biotechnology are not aimed at the production of genetic abnormalities, but rather mimic advantageous natural results in a very efficient way.
Some of the new and more precise techniques of modern biotechnology in other words blur the line between what is “natural” and what is “unnatural”.
Clear legal criteria should be established in order to identify which results the legislator intends to regulate, and which results not.

241 Idem.
5. Bibliography

Legal sources

Legislation “sensu lato”

International

OECD Guidelines (1986) - Recombinant DNA: Safety Considerations

UNCED Rio de Janeiro Declaration of 1992


The Cartagena Protocol on Biosafety to the Convention on Biological Diversity

EU

Treaty on the Functioning of the European Union, OJ C 83, 30.03.2010

Treaty on the European Union, OJ C 83, 30.03.2010


Commission Regulation (EC) No 641/2004 of 6 April 2004 on detailed rules for the implementation of Regulation (EC) No 1829/2003 of the European Parliament and of the Council as regards the application for the authorisation of new genetically modified food and feed, the notification of existing products and adventitious or technically unavoidable presence of genetically modified material which has benefited from a favourable risk evaluation, OJ L 102, 7.4.2004


Commission Decision 2009/770/EC of 13 October 2009 establishing standard reporting formats for presenting the monitoring results of the deliberate release into the environment of genetically modified organisms, as or in products, for the purpose of placing on the market, pursuant to Directive

Commission Recommendation 2010/01/EC of 13 July 2010 on guidelines for the development of national coexistence measures to avoid the unintended presence of GMOs in conventional and organic crops, *OJ C 200, 22.07.2010*


*Preparatory documents, communications*

EC, “Explanatory memorandum to the proposals for Council Directives on the contained use of genetically modified micro-organisms and on the deliberate release in the environment of genetically modified organisms”, COM(88)6397final (not published)


EC, “Users Guide to European Regulation in Biotechnology”, Contract no. FIF.2004 0828


Jurisprudence


CJEU C-26/62 Van Gend en Loos v Nederlandse Administratie der Belastingen, E.C.R. 1963, 1

CJEU C-6/64 Costa v ENEL, E.C.R. 1964, 585
CJEU C-9/70 Grad v Finanzamt Traunstein, E.C.R. 1970, 825


CJEU C-2/74 Reyners v Belgium, E.C.R. 1974, 631

CJEU C-43/75 Defrenne v SABENA, E.C.R. 1976, 455

CJEU C-51/76 Verbond van Nederlandse Ondernemingen v Inspecteur der Invoerrechten en Accijnzen, E.C.R. 1977, 113


CJEU C-165/84 Krohn v BALM, E.C.R. 1985, 3997

CJEU C-149/85 Wybot v Faure, E.C.R. 1986, 2391

CJEU C-102/86 Apple and Pear Development Council v Commissioners of Customs and Excise, E.C.R. 1988, 1443

CJEU C-186/87 Cowan v Le Trésor public, E.C.R. 1989, 195

CJEU C-187/87 Saarland v Ministre de l'Industrie, E.C.R. 1988, 5013

CJEU C-173/88 Skatteministeriet v Morten Henriksen, E.C.R. 1989, 2763


CJEU C-6/90 Francovich and Bonifaci v Italy, E.C.R. 1991, I-5357


CJEU C-90/92 Dr Tretter v Hauptzollamt Stuttgart-Ost, E.C.R. 1993, I-3569

CJEU C-61/94 Commission v Germany, E.C.R. 1996, I-3989


CJEU C-255/99 Anna Humer, E.C.R. 2002, I-1205


CJEU C-99/00 Criminal proceedings against Kenny Lyckeskog, E.C.R. 2002, I-4839

CJEU C-109/00 Tele Danmark A/S v Handels- og Kontorfunktionoerernes Forbund i Danmark (HK), E.C.R. 2001, I-6993

CJEU C-112/00 Eugen Schmidberger v Republik Österreich, E.C.R. 2003, I-5659

CJEU C-133/00 Bowden and Others v Tufnells Parcels Express Ltd, E.C.R. 2001, I-7031

CJEU C-212/00 Stallone v Office national de l’emploi, E.C.R. 2001, I-7625

CJEU C-400/00 Club-Tour, Viagens e Turismo SA v Goncalves Garrido, E.C.R. 2002, I-4051

CJEU C-45/01 Christoph-Dornier-Stiftung für Klinische Psychologie v Finanzamt Gießen, E.C.R. 2003, I-12911

CJEU C-117/01 KB v National Health Service Pensions Agency and Secretary for Health, E.C.R. 2004, I-541

CJEU C-245/01 RTL Television gmbH v Nudersächsische Landesmedienanstalt für privaten Rundfunk, E.C.R. 2003, I-12489


CJEU C-36/02 Omega Spielhallen v Oberbürgermeisterin der Stadt Bonn, E.C.R. 2004, I-9609


CJEU C-210/06 Cartesio Oktakó és Szolgátató Bt., E.C.R. 2008, I-9641


CJEU C-446/07 Severi v Regione Emilia Romagna, E.C.R. 2009, I-8041
CJEU C-378/08 ERG and Others v Ministerio dello Sviluppo economico, E.C.R. 2010, I-1919

CJEU C-434/08 Harms v Heidinga, E.C.R. 2010, I-4431

CJEU C-578/08 Chakroun v Minister van Buitenlandse Zaken, E.C.R. 2010, I-1839

CJEU C-582/08 Commission v UK, E.C.R. 2010, I-7195

CJEU C-49/09 Commission v Poland, E.C.R. 2010, I-10619

CJEU C-152/09 André Grootes v Amt für Landwirtschaft Parchim, E.C.R. 2010, I-11285


CJEU C-229/09 Hogan Lovells International v Bayer CropScience, E.C.R. 2010, I-11335

CJEU C-442/09 Karl Heinz Bablok and Others v Freistaat Bayern, E.C.R. 2011, I-7417

CJEU C-508/10 Commission v Netherlands, not published yet

CJEU C-281/11 Commission v Poland, not published yet

*Doctrine*


ITZCOVICH, G., *The Interpretation of Community Law by the European Court of Justice*, German Law Journal, p. 539


SCHUTYSE, K., “De Europese regelgeving inzake GGO’s: een stand van zaken”, MER 2006/3, p.1-20

**Other sources**

ACRE advice: New Techniques used in plant breeding, 18 July 2013


COGEM report: ”New techniques in plant biotechnology”, CGM/061024-02


DEBUSSCHERE, B., "Genetisch gecorrigeerde revolutie", De Morgen, 29 July 2014

ERIKSSON, D., STYMNE, S., SCHOERRING, J. K., SCHOUTEN, H., "Correspondence: The Slippery slope of cisgenesis", in Nature Biotechnology, vol. 32, no. 8, august 2014


NEW TECHNIQUES WORKING GROUP Final Report 2012 (not public)

Legal Briefing paper – The regulatory status of plants resulting from New Breeding Techniques, produced by the NBT Platform, April 2014 (not public)

PARISI, C., 2012 "New plant breeding techniques: State-of-the-art, potential and challenges", doctoral thesis biosciences and agri-food sciences University of Córdoba, Spain


oral presentation Prof. Mr. Drs. Pieter van der Meer, CEPM conference, "Revision of the GMO Directive: Reconciling a globalised market with national GMO regulations in the EU. What solutions to ensure the competitiveness and coexistence of sectors?", 9 December 2014, Brussels

Position statement of the ZKBS on new plant breeding techniques, Ref. No. 402.45310.0104, June 2012
6. Nederlandse samenvatting van de masterproef

De moderne biotechnologie is een relatief jonge en snel evoluerende tak van de wetenschap. De techniek van genetische modificatie is een van haar belangrijkste hedendaagse toepassingen.

De EU regelt de techniek van genetische modificatie middels een wetgevend kader dat in 1990 het levenslicht zag.

Dit wetgevend kader bevat onder meer specifieke regels voor de doelbewuste introductie van GGO’s in het milieu, voor de grensoverschrijdende verplaatsing van GGO’s, en voor het gebruik van GGO’s in levensmiddelen en diervoeders.

De laatste jaren zijn er binnen de moderne biotechnologie een aantal nieuwe technieken ontwikkeld die een sneller, meer specifiek en/of meer efficiënt plantveredelingsproces toelaten dan de klassieke technieken van genetische modificatie. Deze technieken worden New (Plant) Breeding Techniques (NBTs) genoemd.

De meeste van deze technieken maken gebruik van een klassieke techniek van genetische modificatie, maar zij resulteren in een ‘gemodificeerd’ organisme dat zo’n precieze en specifieke wijziging heeft ondergaan, dat het niet van een in de natuur voorkomend organisme kan onderscheiden worden.

Gelet op deze technische bijzonderheid, hebben zowel de private als publieke sector herhaaldelijk de vraag gesteld of de organismen die door deze technieken geproduceerd worden, onderworpen zijn aan de voorschriften van het Europees GGO-recht.

De thesis bespreekt enkele door de wetenschappelijke literatuur opgeworpen juridische vragen en gaat in essentie na wat volgens het vigerende EU recht een “GGO” is. De thesis komt tot de conclusie dat deze term verwijst naar een organisme dat geproduceerd is door een techniek van genetische modificatie, en dat daardoor een nieuwe combinatie van genetisch materiaal bevat die niet in de natuur voorkomt.

De GGO definitie verwijst met andere woorden naar zowel een ‘onnatuurlijk’ proces als naar een ‘onnatuurlijk’ resultaat.

In een laatste hoofdstuk bespreekt de thesis verschillende NBTs, en gaat na of deze in het licht van
de besproken GGO-definitie een organisme produceren dat onderworpen is aan de voorschriften van het Europees GGO-recht.