

Are genome-edited micro-organisms covered by Directive 2009/41/EC?—implications of the CJEU’s judgment in the case C-528/16 for the contained use of genome-edited micro-organisms

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ABSTRACT

In its judgement of July 25, 2018, the Court of Justice of the European Union (CJEU) in the case C-528/16, *Confédération paysanne and Others*, held that organisms obtained by techniques of mutagenesis are ‘genetically modified organisms’ (GMOs). It follows from the Court’s reasoning that genome-edited organisms, ie organisms resulting from techniques of directed mutagenesis, are GMOs as well and are fully regulated by Directive 2001/18/EC. However, Directive 2001/18/EC only stipulates rules for the deliberate release and placing on the market of GMOs. By contrast, the European Union (EU) has adopted a separate set of rules laid down in Directive 2009/41/EC, which apply to the so-called ‘contained use’ of ‘genetically modified micro-organisms’ (GMMs). Whether also genome-edited micro-organisms are GMMs and, thus, subject to Directive 2009/41/EC is of crucial importance since contained use activities with genome-edited micro-organisms are currently carried out extensively, eg in laboratories and research facilities. An in-depth legal analysis shows that the CJEU’s interpretation of Directive 2001/18/EC can be extended to Directive 2009/41/EC which means that, in the end, genome-edited micro-organisms are GMMs invariably subject to Directive 2009/41/EC.

KEYWORDS: C-528/16, contained use, Directive 2009/41/EC, Directive 2001/18/EC, EU-regulation, genome-edited

I. INTRODUCTION

I.A. The Issue: Does the CJEU’s Ruling Extend to the Contained Use of GMMs?

Directive ¹2001/18/EC² regulates both the deliberate release into the environment and the placing on the market of GMOs. In its judgement of July 25, 2018, in the case C-528/16, *Confédération paysanne and Others*,³ the CJEU held that organisms obtained by techniques of mutagenesis are ‘genetically modified organisms’ within the meaning of the GMO definition of Directive 2001/18/EC.⁴ It can be deduced from the Court’s decision that genome-edited organisms, ie organisms genetically altered through modern techniques of directed mutagenesis, are GMOs as well. In addition, it can be concluded from the ruling that genome-edited organisms are not exempted from the scope of application of Directive 2001/18/EC under the mutagenesis exemption clause.⁵ Both conclusions can be drawn from the Court’s holding in conjunction with its reasoning and the facts of the case.⁶ Hence, genome-edited organisms are fully governed by Directive 2001/18/EC.⁷

1 This article was created as part of the Bavarian Research Association ‘Interaction of Human Brain Cells’ (ForInter) funded by the Bavarian State Ministry of Science and the Arts (Bayerisches Staatsministerium für Wissenschaft und Kunst).

2 Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC, OJ L 106, 17.4.2001, p. 1.

3 C-528/16, *Confédération paysanne and Others*, 2018 ECLI:EU:C:2018:583.

4 The GMO definition is laid down in Art. 2 (2) Directive 2001/18/EC.

5 The mutagenesis exemption clause is laid down in Art. 3 (1), Annex I B (1) Directive 2001/18/EC.

6 *Confédération paysanne and Others*, *supra* note 3, at paras. 23, 28–29, 38, 47, 51, 53–54.

7 This is, in our opinion, the prevailing view among legal scholars. See, eg René Custers et al., *Genetic Alterations That Do or Do Not Occur Naturally; Consequences for Genome Edited Organisms in the Context of*

As a consequence of the CJEU's ruling, genome-edited organisms are also subject to those EU directives and EU regulations which apply to GMOs and which, at the same time, define GMOs by reference to the GMO definition and the mutagenesis exemption clause of Directive 2001/18/EC.⁸ All these directives and regulations apply to the deliberate release into the environment or the placing on the market of GMOs, respectively.

However, the EU has adopted another set of rules that apply to the so-called 'contained use' of 'genetically modified micro-organisms', eg in laboratories, hospitals, or industrial installations. These rules are laid down in Directive 2009/41/EC.⁹ This directive defines GMMs and its scope of application autonomously, ie not by reference to the GMO definition and the mutagenesis exemption clause of Directive 2001/18/EC.¹⁰ Therefore, the rules on the deliberate release and placing on the market of GMOs, on the one hand, and on the contained use of GMMs, on the other hand, form two distinct legal regimes.

For that reason, it is neither clear nor trivial whether the CJEU's ruling on the interpretation of the GMO definition and the mutagenesis exemption clause of Directive 2001/18/EC extends to Directive 2009/41/EC. This is a delicate question of utmost importance since genome-editing of cells, including human cells, is currently carried out extensively in laboratories for purposes of basic research. In addition, genome-editing via CRISPR/Cas9 has already been used for purposes of ex vivo somatic gene

Regulatory Oversight, 6 FRONT. BIOENG. BIOTECHNOL. 1, at 6 (2019); Stuart J. Smyth, *Regulatory Barriers to Improving Global Food Security*, 26 GLOB. FOOD SEC. 1, at 3 (2020); Jens Kahrmann & Georg Leggewie, *Gentechnikrechtliches Grundsatzurteil des EuGH und die Folgefragen für das deutsche Recht*, 40 NuR 761, at 762 (2018); Elisabeth Andersen & Katharina Schreiber, *Genome Editing' vor dem EuGH und seine Folgen*, 42 NuR 99, at 101 (2020); Martin Wasmer, *Roads Forward for European GMO Policy—Uncertainties in Wake of ECJ Judgment Have to be Mitigated by Regulatory Reform*, 7 FRONT. BIOENG. BIOTECHNOL. 1, at 3 (2019); Bettina Wanner et al., *CJEU Renders Decision on the Interpretation of the GMO Directive*, 14 J. INTELLECT. PROP. LAW PRACT. 90, at 91 (2019); Sigrid Bratlie et al., *A Novel Governance Framework for GMO: A Tiered, More Flexible Regulation for GMOs Would Help to Stimulate Innovation and Public Debate*, 20 EMBO REP. 1, at 1 (2019); Tade Matthias Spranger, *Neue Techniken und Europäisches Gentechnikrecht*, 71 Neue Juristische Wochenschrift 2929, at 2929 (2018); Silja Vöneky, *Legal framework*, in Discussion paper focusing on the scientific relevance of genome editing and on the ethical, legal and societal issues potentially involved 17, at 19 (Ethics Council of the Max Planck Society ed. 2019); Ludwig Krämer, *The Genome Editing Technique Is Covered by Directive 2001/18: Comment on Advocate Bobeks Opinion in Case C-528/16*, at para. 36 (2018). Also the European Commission's Group of Chief Scientific Advisors asserted that 'the Court of Justice of the European Union . . . decided that organisms obtained by the new techniques of directed mutagenesis are genetically modified organisms (GMOs), within the meaning of the Directive 2001/18/EC' and that '[n]ew techniques of directed mutagenesis include gene editing such as CRISPR/Cas9 methodologies' [Statement by the Group of Chief Scientific Advisors, *A Scientific Perspective on the Regulatory Status of Products Derived from Gene Editing and the Implications for the GMO Directive*, at 1 (2018)]. See, however, on a different view, Piet van der Meer et al., *The Status under EU Law of Organisms Developed through Novel Genomic Techniques*, EUR. J. RISK REGUL. 1, at 11 (2021), who opine that the Court's ruling should be construed much more narrowly suggesting, in essence, that it is still unclear whether, and to what extent, genome-edited organisms are covered by Directive 2001/18/EC.

- 8 See Art. 4 (4) Directive 2002/53/EC; Art. 4 (2) Directive 2002/55/EC; Art. 5 (1) Directive 1999/105/EC; Art. 3 (2); Art. 5ba (1) Directive 68/193/EEC; Art. 2 (5) Regulation (EC) No 1829/2003; Art. 3 (16) Regulation (EC) No 1107/2009; Art. 6 (2)(1), Art. 31 (2)(1) Regulation (EC) No 726/2004. Art. 3 (1) Regulation (EC) No 1830/2003; Art. 3 (2) Regulation (EC) No 1946/2003.
- 9 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, OJ L 125, 21.5.2009, p. 75.
- 10 Art. 2 (b), Art. 3 (1)(a), Annex II, Part A (1) Directive 2009/41/EC.

therapy trials which require the prior in vitro preparation of the human genome-edited cells to be administered to the relevant patients.¹¹ Any such usages of genome-edited human cells would have to be classified as contained uses of GMMs subject to Directive 2009/41/EC if genome-edited cells were to be considered to be GMMs within the meaning of that Directive.

I.B. By Way of Example: Contained Use of Genome-edited Human iPSCs

A highly topical example regarding genome-editing of human cells is research on, or research using, genetically modified human induced pluripotent stem cells (iPSCs). These cells have become of utmost scientific interest since they exhibit certain peculiar features. Stem cells are characterized and defined by two main functions¹²: (i) the ability of self-renewal, ie via cell division, they are able to generate daughter cells that have a similar developmental potential as the mother cell¹³ and (ii) the capability of differentiation, ie via cell division, a stem cell can differentiate into a more specialized cell type.¹⁴ Pluripotent stem cells are a special type of stem cells that have infinite self-renewal capacity and can differentiate into all somatic cell types of the mature body of the respective organism.¹⁵

There exist two types of pluripotent stem cells, embryonic stem cells (ESCs) and iPSCs. ESCs are derived from the inner cell mass of the early embryo at the blastocyst stage, which raises various ethical problems since the extraction of ESCs requires, necessarily, an intrusion into the embryo, usually resulting in its destruction.¹⁶ iPSCs, on the other hand, can be obtained by inducing a dedifferentiation of adult somatic cells using several in vitro technologies, known as cell reprogramming.¹⁷ This approach has, inter alia, the advantage that the ethical problems of ESCs do not arise (since embryos are not involved), iPSCs can be produced in virtually unlimited numbers, and patient-specific iPSCs can be created, allowing for autologous somatic cell/gene therapies which minimize, or even exclude, the risk of immunological rejection of the cell transplants.¹⁸

Currently, iPSCs are already used for a vast variety of applications. This includes among others the examinations of gene functions, the study of physiological processes

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- 11 See the most recent report by Haydar Frangoul et al., *CRISPR-Cas9 Gene Editing for Sickle Cell Disease and β -Thalassemia*, 384 N. ENGL. J. MED. 252 (2021), on the successful infusion of autologous genome-edited hematopoietic stem and precursor cells.
 - 12 Douglas Melton & Chad Cowan, 'Stemness': *Definitions, Criteria, Standards*, in 2 HANDBOOK OF STEM CELLS xxiii-xxix, at p. xxiii (Robert Lanza et al. eds., 4th ed. 2004); Amita Sarkar, *Encyclopaedia of Stem Cells 2: Embryonic Stem Cells*, at 236 (2009); Kuldip S. Sidhu et al., *Stem Cells, Definition, Classification and Sources*, in FRONTIERS IN PLURIPOTENT STEM CELLS RESEARCH and THERAPEUTIC POTENTIALS. Bench-to-Bedside 3, at 3 (Kuldip S. Sidhu ed., 2012).
 - 13 Shenghui He et al., *Mechanisms of Stem Cell Self-Renewal*, 25 ANNU. REV. CELL DEV. BIOL. 377, at 378 (2009).
 - 14 Sean J. Morrison et al., *Regulatory Mechanisms in Stem Cell Biology*, 88 Cell 287, at 288 (1997).
 - 15 Richard L. Carpenedo & Todd C. McDevitt, *Chapter II.1.7—Stem Cells: Key Concepts*, in BIOMATERIALS SCIENCE. AN INTRODUCTION TO MATERIALS IN MEDICINE 487, at 488 (Buddy D. Ratner ed., 3rd ed. 2013).
 - 16 J.A. Thomson et al., *Embryonic Stem Cell Lines Derived from Human Blastocysts*, 282 SCIENCE (New York, N.Y.) 1145, at 1145 (1998); S.P. Medvedev et al., *Induced Pluripotent Stem Cells: Problems and Advantages when Applying them in Regenerative Medicine*, 2 ACTA NATURAE 18, at 18 (2010).
 - 17 Antonio Romito & Gilda Cobellis, *Pluripotent Stem Cells: Current Understanding and Future Directions*, 2016 STEM CELLS INT. 9451492, at 2 (2016).
 - 18 Medvedev et al., *supra* note 16, at 25.

during cell development, the analysis of the pathogenesis of human genetic diseases, the testing of drugs, and clinical applications.¹⁹ In fact, eg in Japan, clinical trials with iPSC-derivatives concerning cell therapies of severe and hitherto incurable diseases (such as macular degeneration, Parkinson's Disease, and spinal cord injuries) have already been authorized.²⁰

An even greater potential of iPSCs can be unlocked by using genome-editing, especially by application of the CRISPR/Cas system, to offset existing limitations of iPSCs and to enable new application methods.²¹ In this regard, it is of note that both the reprogramming of somatic cells, especially into iPSCs, and the development of the CRISPR/Cas technology have been awarded Noble Prizes in 2012²² and, most recently, in 2020, respectively.²³ Accordingly, both technologies are ground-breaking, and, therefore, it can be reasonably expected that their combination will unleash unprecedented progress in basic and clinical research as well as medicinal products' development.

Against this background, it is necessary to clarify whether genome-editing of iPSCs is subject to the rules laid down in Directive 2009/41/EC since it is of crucial importance for academic researchers, small biotech companies, and pharmaceutical corporations situated within the EU whether genome-editing of iPSCs and contained uses of genome-edited iPSCs are subject to the restrictions of the EU's gene technology regulations.

If genome-edited iPSCs were classified GMMs subject to Directive 2009/41/EC, their contained use, eg in laboratories or hospitals or in pharmaceutical manufacturing facilities, would be subject to certain administrative requirements. Depending on the level of risk,²⁴ the contained use of GMMs may require prior notification to, or even prior authorization by, the competent administrative authority.²⁵ In addition, the contained use of GMMs must always take place in conformity with certain containment measures that correspond to the level of risk.²⁶ In any case, users of GMMs have to carry out a risk assessment of the contained use as regards risks to human health and the environment possibly arising from the GMMs and their use.²⁷ In addition, users have

19 Romito & Cobellis, *supra* note 17, at 1.

20 D. Cyranoski, *Japan Poised to Allow 'Reprogrammed' Stem-Cell Therapy for Damaged Corneas*, <https://www.nature.com/articles/d41586–019–00860-0> (accessed Feb. 12, 2021). See also the most recent report of Jeffrey S. Schweitzer et al., *Personalized iPSC-Derived Dopamine Progenitor Cells for Parkinson's Disease*, 382 N. ENGL. J. MED. 1926 (2020).

21 Dirk Hockemeyer & Rudolf Jaenisch, *Induced Pluripotent Stem Cells Meet Genome Editing*, 18 CELL STEM CELL 573, at 575 (2016).

22 Noble Prize in Physiology and Medicine for John B. Gurdon and Shinya Yamanaka, their key publications being: J.B. Gurdon, *The Developmental Capacity of Nuclei Taken from Intestinal Epithelium Cells of Feeding Tadpoles*, 10 J. EMBRYOL. EXP. MORPHOL. 622 (1962) and Kazutoshi Takahashi & Shinya Yamanaka, *Induction of Pluripotent Stem Cells from Mouse Embryonic and Adult Fibroblast Cultures by Defined Factors*, 126 CELL 663 (2006).

23 Noble Prize in Chemistry for Emmanuelle Charpentier and Jennifer A. Doudna, their key publication being: Martin Jinek et al., *A Programmable Dual-RNA-Guided DNA Endonuclease in Adaptive Bacterial Immunity*, 337 SCIENCE 816 (2012).

24 On the classification of contained uses of GMMs in four classes (ie class 1: no or negligible risk, class 2: low risk, class 3: moderate risk, and class 4: high risk) see Art. 4 (3) Directive 2009/41/EC.

25 Cf. Art. 6-9 Directive 2009/41/EC.

26 Art. 5 (1), Annex IV Directive 2009/41/EC.

27 Art. 4(2), Directive 2009/41/EC.

to keep records of these risk assessments, which may be inspected by the competent public authorities.²⁸ In practice, these regulatory requirements are often considered as undue bureaucratic burdens unwarranted by potential risks that might arise from the contained use of GMMs.²⁹

The regulatory problem of whether genome-edited iPSCs are GMMs subject to Directive 2009/41/EC is not irrelevant simply because of the fact that iPSCs themselves may constitute GMMs even without having undergone genetic alterations through genome-editing techniques. Admittedly, at the beginning, iPSCs were generated through insertion of transgenes³⁰ and, therefore, undoubtedly, constituted genetically engineered cells. However, since then, methods not requiring viral integration of transgenes have been developed. For example, somatic cells may also be dedifferentiated into iPSCs through delivery of reprogramming proteins only.³¹

I.C. Outline of the Analysis

Our analysis of the regulatory problem³² will take the following steps. First, the use of genome-editing on iPSCs is briefly explained (Section II). Second, the applicability of Directive 2009/41/EC to genome-edited iPSCs is analyzed (Section III). For that purpose, it must be clarified whether human iPSCs can be considered to be ‘micro-organisms’ in accordance with Directive 2009/41/EC (Section III.A) and whether genome-edited human iPSCs are ‘genetically modified micro-organisms’ pursuant to Directive 2009/41/EC (Section III.B). This is followed by an analysis whether at least one of the exemption clauses laid down in Annex II, Part A of the Directive applies to genome-edited iPSCs (Section III.C). After this assessment, the implications for domestic courts (Section IV) can be briefly evaluated.

II. GENOME-EDITED IPSCS

II.A. Genome-editing Techniques

Genome-editing refers to a set of relatively new genetic modification techniques of which the most prominent example is CRISPR/Cas.³³ Generally speaking, these methods allow for the targeting of a specific location in a genome and the modification of the DNA at that specific site. Depending on the exact technique used, genome-editing can be applied to cause random mutations (small insertions or deletions), gene replacements, gene insertions, and predefined deletions or inversions.³⁴ As far as genome-editing techniques produce predefined mutations (ie small insertions or

28 Art. 4(6), Art. 7 sent. 2 Directive 2009/41/EC.

29 Especially, in cases of class 1 or class 2 activities (see *supra* note 24). See, eg Hans-Georg Dederer & Gregor Frenken, *Genom-Editierung am Menschen—Vergleich der regulatorischen Rahmenbedingungen für CRISPR-Gen-Editierung und ihre Auswirkungen auf Forschung und Innovation*, 2021, p. 79 [Studie zum deutschen Innovationssystem Nr. 13-2021, edited by the Expertenkommission Forschung und Innovation (EFI)].

30 Shinya Yamanaka, *A Fresh Look at iPSC Cells*, 137 CELL 13, at 14 (2009).

31 H. Zhou et al., *Generation of Induced Pluripotent Stem Cells Using Recombinant Proteins*, 4 CELL STEM CELL 381 (2009).

32 Whether the CJEU’s judgment of July 25, 2018, in the case C-528/16 extends to the contained use regime established by Directive 2009/41/EC and, thus, to genome-edited human cells, especially iPSCs.

33 Other genome-editing techniques are oligonucleotide-directed mutagenesis (ODM) or site-directed nuclease (SDN) techniques using zinc-finger nucleases (ZFNs) or transcription activator-like effector nucleases (TALENs).

34 Shaun J. Curtin et al., *Genome Engineering of Crops with Designer Nucleases*, 5 PLANT GENOME 42, at 42 (2012).

deletions of one or more base pairs only), they can be classified as techniques of directed mutagenesis.

Genome-editing techniques using so-called SDNs, such as the CRISPR/Cas system, can be applied in three different ways called SDN-1, SDN-2, and SDN-3.³⁵ SDN-1 causes a site-specific double-strand break (DSB) of the cell's DNA. This break is repaired by the cell's own natural repair mechanism causing a random mutation at that predefined site. In the case of SDN-2, in addition to the SDN system, a small repair-DNA-template is introduced into the cell to create a site-specific predefined mutation. The cell's repair mechanism fixes the DSB by copying the genetic information from the template into the cell. The result is a genetic alteration, where the DSB used to be, consistent with the genetic sequence of the template. SDN-3 is used to stably integrate external genetic material into the cell. For that purpose, a larger piece of donor DNA is introduced into the cell together with the SDN system. The cell's own repair mechanism inserts then the donor DNA at the locus of the DSB.

It is especially the potential to alter the genome at a predefined locus and therefore in a site-specific manner that distinguishes genome-editing from traditional genetic engineering techniques. Additionally, especially CRISPR/Cas is also way faster, more cost-effective, and can be applied more efficiently than earlier genetic engineering and genome-editing techniques.³⁶

II.B. Genome-editing of Human iPSCs

Genome-editing combined with iPSC-technology opens up a range of new application possibilities and allows to improve the existing application scenarios of iPSCs not just in research but also in therapy.

The site-specific targeted applicability of genome-editing provides, for example, the opportunity to overcome the resilience of human iPSCs to conventional gene targeting methods.³⁷ At the same time, genome-editing of human iPSC can be used for more advanced disease modeling and drug development.³⁸ This allows not only a better understanding of gene functions, cell interactions, or the underlying genetic alterations causing certain diseases but facilitates also the development of new testing methods for novel drugs. Furthermore, efficient and specific gene targeting via genome-editing

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- 35 Regarding this and the following see Thorben Sprink et al., *Regulatory Hurdles for Genome Editing: Process- vs. Product-based Approaches in Different Regulatory Contexts*, 35 *PLANT CELL REP.* 1493, at 1497 (2016); Aftab Ahmad et al., *Regulatory, Ethical, and Social Aspects of CRISPR Crops*, in *CRISPR CROPS. THE FUTURE OF FOOD SECURITY* 261, at 271 (Aftab Ahmad et al. eds., 2020); Sarah Z. Agapito-Tenfen et al., *Revisiting Risk Governance of GM Plants: The Need to Consider New and Emerging Gene-Editing Techniques*, 9 *FRONT. PLANT SCI.* 1, at 4 (2018); Jeffrey D. Wolt et al., *The Regulatory Status of Genome-Edited Crops*, 14 *PLANT BIOTECHNOL. J.* 510, at 514 (2016).
- 36 Samantha A. M. Young et al., *Advantages of Using the CRISPR/Cas9 System of Genome Editing to Investigate Male Reproductive Mechanisms Using Mouse Models*, 17 *ASIAN J. ANDROLOGY* 623, at 624 (2015); Patrick D. Hsu et al., *Development and Applications of CRISPR-Cas9 for Genome Engineering*, 157 *CELL* 1262, at 1263 (2014); Darjus F. Tschaharganeh et al., *Using CRISPR/Cas to Study Gene Function and Model Disease In Vivo*, 283 *FEBS J.* 3194, at 3194 (2016).
- 37 Hockemeyer & Jaenisch, *supra* note 21, at 575.
- 38 Claudia de Masi et al., *Application of CRISPR/Cas9 to Human-Induced Pluripotent Stem Cells: From Gene Editing to Drug Discovery*, 14 *HUM. GENOMICS* 1 (2020); Ronen Ben Jehuda et al., *Genome Editing in Induced Pluripotent Stem Cells Using CRISPR/Cas9*, 14 *STEM CELL REV. REP.* 323, at 325 (2018).

make new types of therapeutic applications of human iPSCs, ie combined cell/gene therapies, feasible.³⁹

These are only examples of the wide array of current and envisaged applications of genome-edited iPSCs. Even though the significance of genome-edited iPSCs for research and therapy cannot be conclusively determined yet, there is no doubt that it will play a formative role in future medical advances. This makes the regulatory framework for this technology all the more crucial.

III. ARE GENOME-EDITED HUMAN IPSCS SUBJECT TO THE CONTAINED USE REGIME?

Directive 2009/41/EC regulates, pursuant to Art. 1, the contained use of GMMs in the EU. For the contained use regime established by Directive 2009/41/EC to be applicable to genome-edited iPSCs (i) those cells must constitute ‘micro-organisms’, (ii) the micro-organism must be ‘genetically modified’, and (iii) no exemption clause applies.

III.A. iPSCs as ‘Micro-organisms’

1. Cells as ‘Micro-organisms’

Pursuant to Art. 2 (a) Directive 2009/41/EC, the legal term ‘micro-organism’ refers to ‘any microbiological entity, cellular or non-cellular, capable of replication or of transferring genetic material, including viruses, viroids, and animal and plant cells in culture.’ At this point, it should be emphasized that the legal definition of ‘micro-organism’ used by Directive 2009/41/EC differs in part significantly from the biological understanding of that term. In general, a micro-organism is—from a biological point of view—understood as an organism too small to be seen by the human eye due to its microscopic or submicroscopic size.⁴⁰ Beyond that, it is contentious whether, eg viruses or plasmids are micro-organisms as well.⁴¹

The definition given by Directive 2009/41/EC reflects in part a broader understanding of the term ‘micro-organism.’ First of all, it expressly declares viruses and viroids to be micro-organisms, so the biological controversy over their classification is of no significance here. However, even more noteworthy, the definition explicitly encompasses animal and plant cells as well, although it might seem rather nonsensical that a single cell of a multicellular organism can, in itself, constitute an organism.⁴² This can be explained by the fact that the GMM definition is mainly risk-based. Therefore, cells or cell cultures are covered as well, if genetically modified, because they could possibly develop a pathogenic potential as a consequence of their genetic modification depending on the donor and recipient (micro-)organism, the inserted transgene and the vector used.⁴³

39 Joseph Collin & Majlinda Lako, *Concise Review: Putting a Finger on Stem Cell Biology: Zinc Finger Nuclease-Driven Targeted Genetic Editing in Human Pluripotent Stem Cells*, 29 *STEM CELL* 1021, at 1031 (2011).

40 JANE TAYLOR, *MICROORGANISMS AND BIOTECHNOLOGY*, at 6 (2nd ed., 2001); K. R. ANEJA, *EXPERIMENTS IN MICROBIOLOGY, PLANT PATHOLOGY AND BIOTECHNOLOGY*, at 1 (4th ed., 2003).

41 PAUL SINGLETON & DIANA SAINSBURY, *DICTIONARY OF MICROBIOLOGY AND MOLECULAR BIOLOGY*, at 477 (3rd ed., 2006).

42 GRAHAM DUTFIELD, *INTELLECTUAL PROPERTY, BIOGENETIC RESOURCES AND TRADITIONAL KNOWLEDGE*, at 29 (2004).

43 See the elements of a risk assessment regarding contained uses of GMMs according to Art. 4 (2), Annex III Directive 2009/41/EC.

Consequently, against the backdrop of the definition of the term micro-organism in Art. 2 (a) Directive 2009/41/EC, cells—and therefore stem cells and iPSCs—constitute ‘cellular’ ‘microbiological entities’ within the meaning of that definition. Moreover, via cell division, stem cells including iPSCs are ‘capable of replication’. The question that remains to be clarified is, therefore, whether the GMM definition extends also to human cells since it covers expressly ‘animal and plant cells’ only.

2. In Particular: Human Cells as ‘Micro-organisms’

What speaks against the classification of human cells as micro-organisms is that the definition of GMMs explicitly includes animal and plant cells but does not mention human cells. By implication, the GMM definition might not extend to human cells (‘argumentum e contrario’). If the legislator had intended that the GMM definition covers human cells as well, it stands to reason that the legislator would have mentioned them next to plant and animal cells. This point of view can, however, be contested, since the wording indicates a non-exhaustive enumeration (‘including’). Hence, the GMM definition provides a list of examples of entities which constitute, from the legislator’s normative perspective, micro-organisms. Consequently, even if human cells are not explicitly listed, they could still be covered by the definition. In this case, the interpretative maxim ‘eiusdem generis’ can be applied, which means that if a provision refers to a non-exhaustive list of objects to which it applies, the provision extends to other objects which are ‘of the same kind’ as well. It follows that the GMM definition extends to human cells as far as they are comparable to animal and plant cells in view of the object and purpose of Directive 2009/41/EC. The Directive’s purpose is to protect human health and the environment.⁴⁴ With regard to the possible pathogenic potential arising from artificial genetic modification, human cells are no different from plant or animal cells. Hence, the risks to health and the environment assumed for the genetic modification of plant and animal cells may also arise in human cells. Therefore, Directive 2009/41/EC should extend to human cells as well.⁴⁵

On the other hand, when systematically compared with Directive 2001/18/EC on the release of GMOs, it is noteworthy that pursuant to recital 15 of Directive 2001/18/EC, ‘human beings should not be considered as organisms’ with a view to the GMO definition. Hence, under the GMO definition laid down in Art. 2 (2) Directive 2001/18/EC, humans are explicitly excluded from the term ‘genetically modified organism (GMO)’. This might point, at first glance, into the direction that human cells are not covered by the GMM definition of Directive 2009/41/EC either since both directives were designed to complement each other in the form of a holistic regulatory framework encompassing all stages, or steps, from research and development until marketing of genetically modified products.⁴⁶ However, the exclusion of human beings

44 Art. 1 Directive 2009/41/EC.

45 In the end, this interpretation coincides with a broad reading of the wording ‘animal cells’ as meaning ‘both human and non-human animal cells’. Such a broad reading may be derived from a biological understanding of the term ‘animal’ which may, from a biological point of view, include ‘humans’ as a particular animal species.

46 Hans-Georg Dederer, *Options for the Regulation of Genome Edited Plants—Framing the Issues*, in *GENOME EDITING IN AGRICULTURE. BETWEEN PRECAUTION AND RESPONSIBILITY* 77, at 80 (Christian Dürnberger et al. eds., 2019). Cf. also the step-by-step approach enshrined in recital 24 of Directive 2001/18/EC: ‘The introduction of GMOs into the environment should be carried out according to the “step by step” principle.’

from the scope of Directive 2001/18/EC has rather ethical and practical reasons since it is legally and ethically inconceivable to regulate the ‘deliberate release’ of genetically modified human beings into the environment. Otherwise, human beings, eg patients after transplantation of genetically modified cells in the course of a somatic gene therapy, would be, just like plants and animals, objects of the law and, in particular, of administrative decisions such as deliberate release approvals. These moral and legal problems do not arise when it comes to regulating human cells in vitro.

Taking all these arguments together, we conclude that human cells and, therefore, especially human iPSCs are micro-organisms within the meaning of Art. 2 (a) Directive 2009/41/EC.

III.B. Genome-edited Human iPSCs as ‘GMMs’

1. ‘Product-based’ Interpretation versus ‘Process-based’ Interpretation

For Directive 2009/41/EC to be applicable to genome-edited human iPSCs, those cells must not just constitute micro-organisms but GMMs. Pursuant to Art. 2 (b) Directive 2009/41/EC, ‘genetically modified micro-organism’ means ‘a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination’. It, therefore, remains to be determined whether the genetic material of genome-edited human iPSCs has been ‘altered in a way that does not occur naturally by mating and/or natural recombination’.

However, this choice of words fails to clarify whether it is crucial that the induced genetic modification, ie the resultant new combination of genetic material within the genome, does not exist in nature or that the process used to produce the genetic modification does not occur naturally. Since the first interpretative option is linked to the characteristics of the end-product (ie the result), it is referred to as ‘product-based interpretation’ (or rather: ‘result-based interpretation’), while the latter is framed ‘process-based interpretation’.⁴⁷

The significance of these different interpretational approaches becomes apparent when one considers the practical implications against the backdrop of genome-editing. Certain genome-editing methods, especially SDN-1 and SDN-2 techniques or ODM, lead, or may lead, to genetic alterations that are indistinguishable from naturally occurring mutations.⁴⁸ Consequently, human iPSCs genetically modified via those techniques would not give rise to GMMs if the product-based interpretation is applied since an organism with exactly the same genetic alteration could occur in nature as well (eg due to ultraviolet radiation of the sun or in the course of ordinary natural cell division). However, if the process-based interpretation is adopted, every genetic alteration induced via genome-editing would lead to a GMM because genome-editing is a highly artificial way of genetic modification that, obviously, does not take place naturally.

This means that the containment of GMOs is reduced and the scale of release increased gradually, step by step, but only if evaluation of the earlier steps in terms of protection of human health and the environment indicates that the next step can be taken.

⁴⁷ *Id.* at 100.

⁴⁸ Ahmad et al., *supra* note 35, at 271; Francesca Taranto et al., *Biotechnological and Digital Revolution for Climate-Smart Plant Breeding*, in *MOLECULAR GENETICS, GENOMICS AND BIOTECHNOLOGY OF CROP PLANTS BREEDING* 37, at 46 (Søren Kjærsgaard Rasmussen ed., 2020); ROGER HULL ET AL., *GENETICALLY MODIFIED PLANTS: ASSESSING SAFETY AND MANAGING RISK*, at 144 (2nd ed., 2021).

Both aforementioned interpretative approaches seem to be justifiable and defensible, but there is no ultimately conclusive evidence to support one over the other. Interestingly, the same interpretative uncertainty existed with regard to the GMO definition of Directive 2001/18/EC.⁴⁹ It is of note that the Court in its judgement of July 25, 2018, in the case C 528/16 did not address this interpretative controversy at all, though.

Although the CJEU's judgment of July 25, 2018, in case C-528/16 concerning the interpretation of the GMO definition of Directive 2001/18/EC⁵⁰ is not directly applicable to the interpretation of the GMM definition of Directive 2009/41/EC, it has a decisive bearing on the interpretation of that definition and, therefore, on the question of whether the contained use regime applies to genome-edited human iPSCs.

2. Hypothesis

Both directives use almost exactly the same wording and structure to define a genetically modified (micro-)organism as shown in Table 1.

Consequently, it can be reasonably hypothesized that the interpretation of the GMO definition under Directive 2001/18/EC by the CJEU in case C-528/16 ought

Table 1. Juxtaposition of GMO definition in Directive 2001/18/EC and GMM definition in Directive 2009/41/EC.

Directive 2001/18/EC	Directive 2009/41/EC
Art. 2	Art. 2
...	...
(2) 'genetically modified organism (GMO)' means an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;	(b) 'genetically modified micro-organism' (GMM) means a micro-organism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination;
Within the terms of this definition:	within the terms of this definition:
(a) genetic modification occurs at least through the use of the techniques listed in Annex I A, part 1;	(i) genetic modification occurs at least through the use of the techniques listed in Annex I, Part A;
(b) the techniques listed in Annex I A, part 2, are not considered to result in genetic modification.	(ii) the techniques listed in Annex I, Part B, are not considered to result in genetic modification;
...	...

49 René Custers, *When Is an Organism Subject to the Provisions of the EU GMO Legislation? An In-Depth Analysis*, at 2 (2016); Bundesamt für Verbraucherschutz und Lebensmittelsicherheit, *Opinion on the Legal Classification of New Plant Breeding Techniques, in Particular ODM and CRISPR-Cas9*, at 3 (2017); Sam Callebaut, *New Developments in Modern Biotechnology: A Survey and Analysis of the Regulatory Status of Plants Produced through New Breeding Techniques*, at 42 (2015); Ludwig Krämer, *Legal Questions Concerning New Methods for Changing the Genetic Conditions in Plants*, at 4 (2015); Tade Matthias Spranger, *Legal Analysis of the Applicability of Directive 2001/18/EC on Genome Editing Technologies*, at 41 (2015).

50 On the binding effect of the Court's judgment, see *infra* note 120.

to be applicable to the GMM definition under Directive 2009/41/EC. This would lead to the conclusion that genome-edited micro-organisms, and hence, genome-edited human iPSCs, were to be considered GMMs within the meaning of Art. 2 (b) Directive 2009/41/EC. In order to verify this hypothesis, a thorough analysis of the Court's reasoning in case C-528/16 is required.

3. CJEU's Interpretation of the GMO Definition [Art. 2 (2) Directive 2001/18/EC]

The CJEU's judgment in case C-528/16 was delivered as a preliminary ruling initiated by a referral from the French Conseil d'État. The Conseil d'État had, *inter alia*, to deal with the question whether plant varieties resulting from so-called mutagenesis techniques, especially obtained through genome-editing, constitute GMOs within the meaning of Art. 2 (2) Directive 2001/18/EC and, if so, whether such plant varieties are exempted from the Directive's scope of application pursuant to Art. 3 (1), Annex I B (1) Directive 2001/18/EC. To be able to make such a determination in line with EU law, the Conseil d'État referred corresponding questions to the CJEU for an authoritative interpretative preliminary ruling in accordance with Art. 267 (1)(b) TFEU.⁵¹

As regards the GMO definition of Art. 2 (2) Directive 2001/18/EC, the CJEU did not make an explicit determination on whether it is to be interpreted in a process- or a product-based manner.⁵² It did not even address the issue that the interpretation of the GMO definition is contentious. Nonetheless, a settlement of this long-lasting dispute among legal scholars can be inferred from the Court's legal argumentation. In that regard, the relevant section of the judgement is the classification of the genome-edited plant varieties as GMOs. This classification is conducted in four distinctive parts: First, the definition of a GMO is reiterated.⁵³ Second, it is examined whether a genetic alteration took place.⁵⁴ Third, a determination is made on whether this alteration can be characterized as not occurring naturally.⁵⁵ And fourth, the final determination is made on whether plant varieties derived through mutagenesis amount to GMOs.⁵⁶ In general, the CJEU adopted within those four steps the position that for an organism to constitute a GMO there must be a product- and a process-based requirement present at the same time.⁵⁷

With regard to the genetic properties of the GMO, it is necessary and sufficient that 'alterations made to the genetic material of an organism' have occurred.⁵⁸ According to the Court, 'mutations brought about by techniques/methods of mutagenesis such as those at issue in the main proceedings' (ie before the French court) constitute such alterations.⁵⁹ The 'techniques/methods of mutagenesis' relevant in the main proceedings were ODM and SDN techniques.⁶⁰ Since the CJEU does not qualify or specify what are 'mutations' and 'alterations' any further and since the aforementioned

51 *Confédération paysanne and Others*, *supra* note 3, at para. 25.

52 See *supra* after note 49.

53 *Confédération paysanne and Others*, *supra* note 3, at para. 27.

54 *Id.* at para. 28.

55 *Id.* at para. 29.

56 *Id.* at para. 30.

57 *Id.* at paras. 28 and 29.

58 *Id.* at para. 28.

59 *Id.*

60 *Id.* at para. 23.

techniques (ODM and SDN), which the Court explicitly referred to, may change a single base pair only, it stands to reason that any genomic change, even a mere point mutation, is sufficient in order to meet the product-based (or: result-based) requirement. Consequently, starting from the phrase ‘altered in a way that does not occur naturally by mating and/or natural recombination’, the CJEU considers only the word ‘altered’ to refer to the resultant genetic properties of the organism. This already implies that the remainder of the phrase is going to be subject to a processed-based interpretation.

In line with this, the Court then states that because ‘those techniques/methods⁶¹ [...] involve the use of genetic engineering, those techniques/methods alter the genetic material of an organism in a way that does not occur naturally, within the meaning of that provision.’⁶² What is noteworthy here is, that the Court completely disregards the specific genetic alteration caused and focuses only on the technique used for inducing the genetic alteration. This does not leave room for any conclusion other than that the CJEU interprets the phrase ‘in a way that does not occur naturally by mating and/or natural recombination’ in a purely processed-based fashion.⁶³ Accordingly, the interpretation of the CJEU in case C-528/16 can be considered to be the turning point that tips the scales in favor of a—primarily—process-based interpretation.⁶⁴

This is reinforced by the Court’s reasoning which is based not only on a linguistic but also on a contextual interpretative approach. Considering the ‘general scheme’ of Directive 2001/18/EC,⁶⁵ the Court took into account that the GMO definition of Art. 2 (2) Directive 2001/18/EC is further specified by two lists of ‘techniques’,⁶⁶ ie processes, which, for purposes of the GMO definition, either result in genetic modifications of organisms (positive list),⁶⁷ leading to GMOs, or not (negative list).⁶⁸

All in all, the CJEU interpreted the GMO definition of Art. 2 (2) Directive 2001/18/EC in such a manner that any resultant genetic alteration will lead to a GMO as long as it is caused by a process, technique, or method, respectively, which does not occur naturally, eg through mating or natural recombination.⁶⁹ Therefore, the Court considered all organisms resulting from mutagenesis techniques, including all genome-editing techniques,⁷⁰ leading to any kind of alteration of the genetic material to be GMOs within the meaning of Art. 2 (2) Directive 2001/18/EC.

61 That is, the ‘techniques/methods of mutagenesis’ relevant in the main proceedings which are, inter alia, ODM and SDN techniques, hence genome-editing techniques (*Id.* at paras. 23 and 28).

62 *Id.* at para. 29.

63 On the same line of thinking: Alan H. Schulman et al., *European Court of Justice Delivers No Justice to Europe on Genome-Edited Crops*, 18 *PLANT BIOTECHNOL. J.* 8, at 9 (2020); Wasmer, *supra* note 7, at 3; Juan Antonio Vives-Vallés & Cécile Collonnier, *The Judgment of the CJEU of 25 July 2018 on Mutagenesis: Interpretation and Interim Legislative Proposal*, 10 *FRONT. PLANT SCI.* 1, at 6 (2019).

64 Similar Felix Beck, *All About That Risk? A (Re-)Assessment of the CJEU’s Reasoning in the ‘Genome Editing’ Case*, 17 *ZEITSCHRIFT FÜR EUROPÄISCHES UMWELT- UND PLANUNGSRECHT (EURUP)* 246, at 249 (2019).

65 *Confédération paysanne and Others*, *supra* note 3, at para. 31.

66 *Id.* at para. 32.

67 Annex Art. 2 (2)(a), Annex I A part 1 Directive 2001/18/EC.

68 Art. 2 (2)(b), Annex I A part 2 Directive 2001/18/EC.

69 Cf. Art. 2 (2) Directive 2001/18/EC.

70 *Confédération paysanne and Others*, *supra* note 3, at paras. 23, 28, 29, and 38.

The Court confirmed this result with reference to the mutagenesis exemption clause [Art. 3 (1), Annex I B (1) Directive 2001/18/EC]. According to that provision, the Directive 'shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B' which, in turn, refers, *inter alia*, to 'mutagenesis'. Arguably, and justifiably from a methodological point of view, the Court made the argument that, if mutagenesis organisms are excluded from the Directive's scope of application, they must have been included as GMOs via the GMO definition beforehand.⁷¹ In fact, the GMO definition [Art. 2 (2) Directive 2001/18/EC] is the 'front door' prompting organisms to enter the regulatory framework of Directive 2001/18/EC, whereas the mutagenesis exemption clause [Art. 3 (1), Annex I B (1) Directive 2001/18/EC] is the 'back door' allowing organisms to escape from the Directive's regime. What may exit through the 'back door' must have been inside before, ie must have passed the 'front door'. Again, be it the 'back door' or the 'front door', it is the technique of mutagenesis, ie the process, that matters in the first place which reinforces our argument that the Court relied on a primarily process-based interpretation of the GMO definition of Art. 2 (2) Directive 2001/18/EC.

4. Applicability of the CJEU's Interpretation to the GMM Definition (Art. 2 (b) Directive 2009/41/EC)

It must be kept in mind that the preliminary ruling in Case C-528/16 did not address the interpretation of Directive 2009/41/EC directly because the interpretation of that Directive was not the subject of the preliminary proceeding. This raises the question whether and, if so, to what extent the interpretation of the CJEU is nonetheless applicable.

With regard to the interpretation of the GMO definition, the CJEU relied exclusively on the wording of Art. 2 (2) Directive 2001/18/EC⁷² and the 'general scheme of that directive'.⁷³ Accordingly, the Court applied the linguistic and contextual interpretative approach. It did not refer to the methods of teleological or historical interpretation.

It has already been pointed out that the wording of the GMO definition in Directive 2001/18/EC and of the GMM definition in Directive 2009/41/EC are more or less identical.⁷⁴ The same holds true for the 'general scheme', or structure, of both definitions. The GMM definition laid down in Directive 2009/41/EC is framed exactly in the same structural manner as the GMO definition in Directive 2001/18/EC, ie the GMM definition is, like the GMO definition, further illustrated by two lists: a positive list of techniques resulting in genetic modifications⁷⁵ and a negative list of techniques not resulting in genetic modifications.⁷⁶

What is more, both Directives, ie 2001/18/EC and 2009/41/EC, contain a mutagenesis exemption clause excluding (micro-)organisms genetically modified through mutagenesis techniques from their respective scope of application. Also in

71 *Id.* at paras. 37–38.

72 *Id.* at paras. 27–30.

73 *Id.* at paras. 31–37.

74 See *supra* section III.B.2, especially Table 1.

75 Art. 2 (b)(i), Annex I, Part A Directive 2009/41/EC.

76 Art. 2 (b)(ii), Annex I, Part B Directive 2009/41/EC.

this regard, wording and ‘general scheme’ of both Directives are practically identical as shown in [Table 2](#).

Table 2. Juxtaposition of the mutagenesis exemption clauses in Directive 2001/18/EC and in Directive 2009/41/EC.

Directive 2001/18/EC	Directive 2009/41/EC
Art. 3	Art. 3
1. This Directive shall not apply to organisms obtained through the techniques of genetic modification listed in Annex I B. ...	1. Without prejudice to Article 4(1), this Directive shall not apply: (a) where genetic modification is obtained through the use of the techniques/methods listed in Annex II, Part A; ...
Annex I B	Annex II, Part A
Techniques/methods of genetic modification yielding organisms to be excluded from the Directive, on the condition that they do not involve the use of recombinant nucleic acid molecules or genetically modified organisms other than those produced by one or more of the techniques/methods listed below are: (1) mutagenesis, ...	Techniques or methods of genetic modification yielding micro-organisms to be excluded from this Directive on condition that they do not involve the use of recombinant-nucleic acid molecules or GMMs other than those produced by one or more of the techniques/methods listed below: 1. Mutagenesis. ...

Hence, Directive 2009/41/EC follows the exactly same regulatory pattern as Directive 2001/18/EC by establishing a GMM definition as the ‘front door’ [Art. 2 (b) Directive 2009/41/EC] and a mutagenesis exemption clause as the ‘back door’ [Art. 3 (1), Annex II Part A (1) Directive 2009/41/EC]. Accordingly, the reasoning by the CJEU in case C-528/16 regarding the GMO definition of Directive 2001/18/EC is applicable in regard to the GMM definition of Directive 2009/41/EC as well: if mutagenesis micro-organisms are able to evade regulation by escaping through the ‘back door’ (ie the mutagenesis exemption clause), they must have passed the ‘front door’ (ie the GMM definition) first. Hence, micro-organisms obtained through mutagenesis, especially through novel techniques of directed mutagenesis such as genome-editing techniques, are GMMs.

Due to the identical wording and the identical regulatory structure (‘general scheme’) of the Directives, the interpretation of the CJEU in case C-528/16 regarding the GMO definition of Art. 2 (2) Directive 2001/18/EC, which was based on both wording and context of said definition, is therefore applicable to the GMM definition of Art. 2 (b) Directive 2009/41/EC as well. For lack of indicators to the contrary, this

leads to the conclusion that the GMM definition has to be interpreted in the same way, especially in the light of a process-based interpretative approach, as the GMO definition.

Consequently, genome-edited iPSCs are to be considered GMMs within the meaning of Art. 2 (b) Directive 2009/41/EC.

III.C. Genome-edited Human iPSCs as GMMs Exempted from the Contained Use Regime?

GMMs which have been created by the use of certain techniques or methods of genetic modification may nonetheless be excluded from the scope of application of the Directive pursuant to Art. 3 (1), Annex II, Part A Directive 2009/41/EC. The respective techniques allowing for an escape of GMMs through the ‘back door’ are listed in Annex II, Part A Directive 2009/41/EC.

1. *Mutagenesis Exemption, Annex II, Part A (1) Directive 2009/41/EC*

According to Art. 3 (1), Annex II, Part A Directive 2009/41/EC, the Directive does not apply to GMMs obtained through ‘mutagenesis’. The term ‘mutagenesis’ is not defined in Directive 2009/41/EC. Generally, the term mutagenesis refers to the formation of a genetic mutation,⁷⁷ while mutation is understood as a ‘stable, and heritable, change in the nucleotide sequence in DNA’.⁷⁸ A genetic mutation can either occur spontaneously in nature or be induced artificially. Traditionally, mutagens, eg chemical agents or ionizing radiation, have been used to provoke random mutations. By contrast, modern genome-editing techniques may induce highly directed mutations, eg site-specific point mutations altering one or a few base pairs of the DNA only. This raises the question whether mutations generated via genome-editing are covered by the mutagenesis exemption as well.

Regarding the interpretation of the mutagenesis exemption, the CJEU’s ruling in case C-528/16 might again provide interpretative guidance since both directives exclude GMMs/GMOs produced via mutagenesis from their respective scope of application in parallel [Annex I B (1) Directive 2001/18/EC and Annex II, Part A (1) Directive 2009/41/EC].⁷⁹

CJEU’s Interpretation of the Mutagenesis Exemption Clause of Art. 3 (1), Annex I B (1) Directive 2001/18/EC It can be inferred from the Court’s judgment that the exemption of organisms produced via mutagenesis [Art. 3 (1), Annex I B (1) Directive 2001/18/EC] is not applicable to organisms obtained by means of genome-editing. On the way to this result, the CJEU first held that ‘by referring generally to mutagenesis, that provision does not, on its own, provide any conclusive guidance as to the types of techniques/methods that the EU legislature intended specifically to exclude from the scope of the directive’.⁸⁰ Hence, the wording is in itself inconclusive.

77 C. W. Theodorakis, *Mutagenesis*, in *ENCYCLOPEDIA OF ECOLOGY* 2475, at 2475 (Sven Erik Jørgensen ed., 1st ed. 2008).

78 PAUL SINGLETON, *DICTIONARY OF DNA AND GENOME TECHNOLOGY*, at 279 (3rd ed., 2013).

79 See *supra* Table 2.

80 *Confédération paysanne and Others*, *supra* note 3, at para. 43.

Turning to a contextual interpretation, the CJEU took note of recital 17 of Directive 2001/18/EC which states that the directive ‘should not apply to organisms obtained through certain techniques of genetic modification which have conventionally been used in a number of applications and have a long safety record’. Based on this intention of the legislature, the CJEU held that only ‘organisms obtained by means of techniques/methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of that directive.’⁸¹ In its reasoning, the Court specified this holding by stating that, therefore, ‘organisms obtained by means of new techniques/methods of mutagenesis which have appeared or have been mostly developed since Directive 2001/18 was adopted’ cannot be considered to be exempted.⁸² Furthermore, the Court explicitly ‘pointed out that the referring court is called upon to rule, in particular, on the techniques/methods of directed mutagenesis involving the use of genetic engineering which have appeared or have been mostly developed since Directive 2001/18 was adopted.’⁸³ In line with the submissions of the referring French court, among these techniques are ‘directed mutagenesis techniques/methods applying new genetic engineering techniques, such as oligonucleotide-directed mutagenesis (ODM) or (site-)directed nuclease (SDN) mutagenesis’,⁸⁴ ie genome-editing techniques. As a result, genome-edited organisms are GMOs which are not exempted via the mutagenesis exemption clause.

The CJEU additionally underpinned this restrictive interpretation of the mutagenesis exemption clause with the precautionary principle and the directive’s objective to protect human health and the environment.⁸⁵

Applicability of the CJEU’s Interpretation to the Mutagenesis Exemption Clause of Art.

3 (1), Annex II, Part A (1) Directive 2009/41/EC It is an intricate question whether the rationale of the CJEU’s judgment on the meaning of the mutagenesis exemption clause of Directive 2001/18/EC can be applied to the mutagenesis exemption clause of Directive 2009/41/EC. In case C-528/16, the CJEU’s considerations regarding the interpretation of the mutagenesis exemption is essentially not based on the wording⁸⁶ but rather on the context,⁸⁷ the objective,⁸⁸ and the interpretative maxim that exemptions must be interpreted strictly.⁸⁹ Consequently, it must be determined whether this argumentative basis for the CJEU’s ruling is also present in Directive 2009/41/EC.

1. **Strict Interpretation.** The CJEU ruled that the mutagenesis exemption clause laid down in Art. 3 (1), Annex I B (1) Directive 2001/18/EC must be interpreted strictly because it is an exception to the obligations stipulated by Directive 2001/18/EC.⁹⁰ The CJEU made this decision not in isolation but based on its previous case law.⁹¹ It can be

81 *Id.* at para. 54.

82 *Id.* at para. 51.

83 *Id.* at para. 47.

84 *Id.* at para. 23.

85 *Id.* at para. 52.

86 Since the Court considered the wording to be inconclusive: *Id.* at paras. 42 and 43.

87 *Id.* at paras. 42, 44–51.

88 *Id.* at paras. 42, 52–53.

89 *Id.* at para. 41.

90 *Id.* at para. 41.

deduced from this that the CJEU considers the narrow interpretation of exceptions as an interpretative principle of EU law.

Hence, the interpretative maxim that exceptions have to be construed strictly and, thus, as a rule narrowly⁹² applies to the mutagenesis exemption clause of Directive 2009/41/EC as well since, obviously, also Art. 3 (1), Annex II, Part A Directive 2009/41/EC is just like Art. 3 (1), Annex I B Directive 2001/18/EC an exemption clause. What deserves closer scrutiny, therefore, is whether the Directives' objectives and contexts are sufficiently similar to translate the CJEU's interpretation of the mutagenesis exemption clause of Directive 2001/18/EC into an identical interpretation of the mutagenesis exemption clause of Directive 2009/41/EC.

2. Teleological and Contextual Interpretation. a. Uniform Risk-based Interpretative Approach. It needs to be emphasized from the outset, and before delving into a more detailed discussion, that, in the present case, both interpretative approaches, ie the objective-based (teleological) interpretation and the context-based (contextual) interpretation, depend decisively and genuinely on a particular perception of the risks associated with novel methods of directed mutagenesis such as genome-editing. Without questioning the submissions of the referring French court, the CJEU accepted that environmental and health risks linked to genome-editing or genome-edited organisms, respectively, 'have not thus far been established with certainty'⁹³ and 'might prove to be similar to those which result from . . . transgenesis',⁹⁴ ie classic genetic engineering inserting 'transgenes' (ie genes from a non-crossable or unrelated species) into the genome of the recipient organism. It suggests itself that, from such a starting point, it is in the end a straight forward conclusion that genome-edited organisms must be kept within the framework governing GMOs, ie must not be allowed to escape through the 'back door' opened by the mutagenesis exemption clause since it is only the GMO regulatory framework which ensures that a thorough case-by-case in advance risk assessment is carried out before genome-edited organisms are used.

Admittedly, the risk-related assumptions of the CJEU in case C-528/16 prompted harsh criticism, especially by scientists.⁹⁵ However, it does not appear from the reasoning that the Court itself has made an own ascertainment of the risk potential of genome-edited organisms, eg on the basis scientific expert evidence. Rather, in line with the idiosyncrasies of the preliminary ruling procedure pursuant to Art. 267 (1)(b) TFEU, the Court simply relied on the facts as presented by the referring French court. Whether

91 C-239/04, *Commission of the European Communities v. Portuguese Republic*, 2006 ECLI:EU:C:2006:665, at Para. 35; C-304/05, *Commission of the European Communities v. Italian Republic*, 2007 ECLI:EU:C:2007:532, at Para. 82; C-182/10, *Marie-Noëlle Solvay and Others v. Région wallonne*, 2012 ECLI:EU:C:2012:82, at Para. 73; C-399/14, *Grüne Liga Sachsen eV and Others v. Freistaat Sachsen*, 2016 ECLI:EU:C:2016:10, at Para. 73; Joined Cases C-387/15 and C-388/15, *Hilde Orleans and Others v. Vlaams Gewest*, 2016 ECLI:EU:C:2016:583, at Para.60; C-441/17, *European Commission v. Republic of Poland*, 2018 ECLI:EU:C:2018:255, at Para. 189.

92 Cf. also the maxim *singularia non sunt extendenda*.

93 *Confédération paysanne and Others*, *supra* note 3, at para. 47.

94 *Id.* at para. 48.

95 Detlef Bartsch et al., *Questions Regarding the Implementation of EU Mutagenesis Ruling in France*, 11 FRONT. PLANT SCI. 584485 (2020); Kahrmann & Leggewie, *supra* note 7, at 762; Fyodor D. Urnov et al., *A Call for Science-Based Review of the European Court's Decision on Gene-Edited Crops*, 36 NAT. BIOTECHNOL. 800 (2018); Schulman et al., *supra* note 63.

the Court, if asked on the interpretation of Directive 2009/41/EC and its applicability to genome-edited micro-organisms, would perceive the risks linked to such organisms any different remains a purely speculative question. Hence, for the time being, it is reasonable to adhere to the Court's risk-related argumentation.

b. The Directive's Objective. In accordance with Art. 1 Directive 2001/18/EC, the CJEU identified the objective of the Directive as to protect human health and the environment when GMOs are released into the environment.⁹⁶ Against that background, the CJEU ruled that 'an interpretation of the [mutagenesis] exemption [clause] . . . without any distinctions, would compromise the objective of protection.'⁹⁷

The meaning of this phrase is that one form of mutagenesis is not just like any other form of mutagenesis, which is why one has to make distinctions between different forms of mutagenesis. Different forms of mutagenesis may raise different risks to human health and the environment, which is why not all mutagenesis organisms can be considered to be excluded automatically from the scope of application of Directive 2001/18/EC. What the Court had in mind (according to our reading of the judgement) was that, according to the submissions of the referring French court, the risks to human health and the environment arising from modern directed mutagenesis techniques were similar to those resulting from GMOs modified through classic genetic engineering introducing foreign genes (so-called 'transgenesis').⁹⁸ Accordingly, from the Court's point of view, organisms obtained by such modern methods of directed mutagenesis could not be equated with organisms obtained through conventional mutagenesis techniques which had been used for decades without identification of risks to human health and the environment⁹⁹ and which, therefore, had been excluded from the Directive's scope right from the beginning.¹⁰⁰ Rather, in the Court's opinion, organisms resulting from mutagenesis techniques developed after adoption of Directive 2001/18/EC on March 12, 2001, had to be treated like ordinary GMOs fully covered by the Directive's regime.¹⁰¹

Turning to Directive 2009/41/EC, its objective is to protect human health and the environment as well (Art. 1 Directive 2009/41/EC). Hence, both Directives, ie 2009/41/EC and 2001/18/EC, equally aim at the protection of human health and the environment. Accordingly, one might conclude that the mutagenesis exemption clause of Directive 2009/41/EC ought to be construed as narrowly as the mutagenesis exemption clause of Directive 2001/18/EC.

On the other hand, the contained use of organisms, eg in laboratories, hospitals, or industrial installations, implies that their contact with the general population and the environment is limited from the outset. One might deduce from this fact that the

96 *Confédération paysanne and Others*, *supra* note 3, at para. 52.

97 *Id.* at para. 53.

98 *Id.* at paras. 24, 48, and 53.

99 *Id.* at paras. 23, 24, 48, and 53.

100 The origins of GMO regulation by the EU date back to 1990 when the first two Directives were adopted: Council Directive 90/219/EEC of 23 April 1990 on the contained use of genetically modified micro-organisms, OJ L 117, 8.5.1990, p. 1; Council Directive 90/220/EEC of 23 April 1990 on the deliberate release into the environment of genetically modified organisms, OJ L 117, 8.5.1990, p. 15. The mutagenesis exemption was laid down in Art. 3, Annex I B (1) Directive 90/219/EEC, Art. 3, Annex I B (1) Directive 90/220/EEC.

101 *Confédération paysanne and Others*, *supra* note 3, at paras. 24, 48, 51, and 53.

mutagenesis exemption clause of the contained use regime established by Directive 2009/41/EC could be interpreted more generously than the comparable clause of Directive 2001/18/EC since contained use takes place, a priori, in confined spaces, which is why such use might guarantee a higher level of protection to human health and the environment compared to the release of (micro-)organisms into the open environment. In fact, recital 4 of Directive 2001/18/EC explicitly spells out the characteristic risks of releases into the environment: ‘Living organisms . . . may reproduce in the environment and cross national frontiers thereby affecting other Member States. The effects of such releases on the environment may be irreversible’. However, it should be borne in mind that the purpose of Directive 2009/41/EC is, pursuant to recital 7, Art. 2 (d) and Annex II B (3.4), to protect human health and the environment also from risks arising from an unintended release, eg in case of an accident. This means that, in the end, both Directives, ie 2009/41/EC and 2001/18/EC, run parallel as regards their objectives. Both Directives aim at the prevention of risks to human health and the environment, especially of such risks which result from (deliberate or accidental) releases of GMOs or GMMs, respectively.

Hence, the teleological interpretation of the mutagenesis exemption clause of Directive 2009/41/EC construing that clause in light of the Directive’s objective should follow the teleological interpretation of the mutagenesis exemption clause of Directive 2001/18/EC by the CJEU in case C-528/16. Accordingly, from a teleological perspective, on the assumption accepted by the CJEU that risks arising from genome-editing are similar to those arising from classic genetic engineering and that these risks ‘have not thus far been established with certainty’¹⁰², GMMs obtained through genome-editing and, thus, genome-edited human iPSCs cannot be considered to be exempted under the mutagenesis exemption clause of Art. 3 (1), Annex II, Part A Directive 2009/41/EC. Rather, they need to undergo prior risk assessment [cf. Art. 4 (2), Annex III sec. A and B Directive 2009/41/EC], which results in a classification of the respective contained use in classes of risk [class 1-4; Art. 4 (3), Annex III Directive 2009/41/EC] which, in turn, leads to an assignment of containment measures [Art. 4 (3), Art. 5, Annex IV Directive 2009/41/EC].

This result is, especially in light of the assumed uncertainties surrounding the risks linked to genome-editing, in compliance with the precautionary principle to which the CJEU referred as well. Admittedly, this principle is not explicitly enshrined in Directive 2009/41/EC, whereas it has been expressly mentioned in recital 8 and Art. 1 Directive 2001/18/EC. However, Directive 2009/41/EC is based on the environmental powers of the EU laid down in Art. 192 (1) TFEU. Since the EU’s environmental policy and, therefore, the EU’s environmental legislation must be based on the precautionary principle [Art. 191 (2)(1) sent. 2 TFEU], any piece of environmental Union law such as Directive 2009/41/EC must be construed in light of the precautionary principle even if it has not been explicitly incorporated into the relevant law.

c. The Directive’s Context. The contextual argumentation relies mainly on recital 17 of Directive 2001/18/EC.¹⁰³ Although the CJEU also refers to the considerations mentioned in recital 4, 5, 8, and 55,¹⁰⁴ it does so only in support of its reasoning in

102 *Id.* at paras. 47 and 48.

103 See *supra* section III.C.1.1. *Id.* at paras. 42, 44–51.

relation to recital 17.¹⁰⁵ Consequently, the question whether or not the consideration of recital 4, 5, 8, and 55 are also reflected in Directive 2009/41/EC can be left aside at this point, since, within the context of the Court's contextual interpretation, they have no independent significance in the Court's reasoning beyond supporting its findings based on recital 17.

Recital 17 expresses the will of the Union legislator that Directive 2001/18/EC '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'. Without giving any reasons, the Court held that this legislative intent formed the ground underlying the mutagenesis exemption clause of Art. 3 (1), Annex I B (1) Directive 2001/18/EC.¹⁰⁶ Premised on the referring French court's submissions, the Court further assumed that the health and environmental risks related to organisms obtained through directed mutagenesis (such as genome-editing) are uncertain¹⁰⁷ and perhaps even similar to those which result from transgenesis¹⁰⁸ and that these novel methods of mutagenesis have been mostly developed since Directive 2001/18/EC was adopted¹⁰⁹ (ie on March 12, 2001). Against this background, it suggests itself that these techniques neither 'have conventionally been used in a number of applications' nor 'have a long safety record' within the meaning of recital 17.

It is of note, that Directive 2009/41/EC does not include a recital similar to recital 17 of Directive 2001/18/EC, though. Even though an equivalent to recital 17 is missing in Directive 2009/41/EC, other contextual arguments could still lead to the conclusion that that the CJEU's rationale is transferable to the interpretation of Directive's 2009/41/EC mutagenesis exemption clause since one may argue that the risk-related concept underlying recital 17 of Directive 2001/18/EC is present in Directive 2009/41/EC as well.

According to the CJEU, the mutagenesis exemption clause in Directive 2001/18/EC is based on the considerations stated in recital 17 of said Directive. Since the same exemption exists in Directive 2009/41/EC, it stands to reason that—even though not mentioned explicitly—the same consideration was the basis for the mutagenesis exemption clause in Directive 2009/41/EC as well. This assumption can be backed by the fact that Directive 2009/41/EC and Directive 2001/18/EC are based on the same blueprint sharing to a significant part their wording, structure, and objective. Besides, both directives form together a uniform framework for the regulation of genetically modified (micro-)organisms, which used to be even more apparent since their predecessors, ie Directives 90/219/EEC and 90/220/EEC, were drafted and adopted in a uniform effort. Therefore, the Court might argue—if asked—that the general GMO/GMM framework is carried by the thought that only GMOs/GMMs derived from traditional mutagenesis techniques should be exempted.

104 *Id.* at paras. 49 and 50.

105 *Id.* at para. 51.

106 See *Id.* at paras. 45 and 46.

107 *Id.* at para. 47.

108 *Id.* at para. 48.

109 *Id.* at para. 47.

Consequently, the absence of a recital equivalent to recital 17 of Directive 2001/18/EC does not hinder the application of the CJEU's rationale stated in case C-528/16 to the mutagenesis exemption clause of Directive 2009/41/EC.

3. Interim Conclusions. Overall, there is a strong case for assuming that the CJEU—if asked—would limit the scope of the mutagenesis exemption clause of Directive 2009/41/EC substantially in the same manner as it did in the case of Directive 2001/18/EC. This means that only 'organisms obtained by means of methods of mutagenesis which have conventionally been used in a number of applications and have a long safety record are excluded from the scope of that Directive.'¹¹⁰

Consequences for the Interpretation of the Mutagenesis Exemption Clause of Directive 2009/41/EC In case C-528/16, the Court held that among these methods of mutagenesis (which 'have conventionally been used in a number of applications and have a long safety record') are 'not' those 'new techniques/methods of mutagenesis which have appeared or have been mostly developed since Directive 2001/18 was adopted',¹¹¹ ie since March 12, 2001. It can be concluded from the Court's reasoning and the facts of the case that among these new mutagenesis techniques are 'directed mutagenesis techniques/methods applying new genetic engineering techniques, such as oligonucleotide-directed mutagenesis or [site-]directed nuclease mutagenesis',¹¹² ie techniques commonly referred to as genome-editing techniques.¹¹³

The question remains whether the same applies to Directive 2009/41/EC, ie whether all methods of directed mutagenesis methods, especially all ODM or SDN mutagenesis techniques are excluded from the scope of the mutagenesis exemption clause of Directive 2009/41/EC as well. The difference is that this Directive was adopted on May 6, 2009, ie approximately 8 years later than Directive 2001/18/EC. Hence, one may reasonably raise the question whether, in 2009, all directed mutagenesis techniques could still be considered techniques which neither 'have conventionally been used in a number of applications' nor 'have a long safety record are excluded from the scope of that Directive.' In fact, certain genome-editing techniques 'have appeared or have been mostly developed' 'before' the adoption date of Directive 2009/41/EC, ie before May 6, 2009. For example, ZFN¹¹⁴ and ODM¹¹⁵ have appeared and have been mostly developed before that date. TALENs have been developed around the adoption date of Directive 2009/41/EC.¹¹⁶ Only the CRISPR/Cas technique which was published for the first time only in 2012 would be clearly out of the mutagenesis exemption clause's scope.

110 *Id.* at para. 54.

111 *Id.* at para. 51.

112 *Id.* at para. 23.

113 See already *supra* sub 3.3.1.1.

114 Aaron Klug, *The Discovery of Zinc Fingers and Their Development for Practical Applications in Gene Regulation and Genome Manipulation*, 43 Q. REV. BIOPHYS. 1 (2010).

115 Noel J. Sauer et al., *Oligonucleotide-Directed Mutagenesis for Precision Gene Editing*, 14 PLANT BIOTECHNOL. J. 496, at 496 (2016).

116 A.A. Nemudryi et al., *TALEN and CRISPR/Cas Genome Editing Systems: Tools of Discovery*, 6 ACTA NATURAE 19, at 20 (2014).

The Court's reference to the adoption date of Directive 2001/18/EC may be interpreted in two different ways. First, it could be assumed that the CJEU makes the argument that techniques established after the Directive was adopted can never be covered by the exemption because the EU legislator had the intention to exempt only those techniques that already existed at the time of adoption (directive's adoption date as cut-off date).¹¹⁷ Second, the mentioning of the Directive's adoption date could be only exemplary for a period of time which, with a view specifically to the genome-editing techniques referred to by the French court, was not sufficient to assume that specifically these techniques 'have conventionally been used in a number of applications' and 'have a long safety record'.

By requiring a 'conventional' use in 'a number of applications' and 'a long safety record', techniques having appeared or having been mostly developed after the Directive's adoption date are, at least 'de facto', excluded from the scope of the mutagenesis exemption clause for a considerable period of time, since, compared to the use of conventional methods of random mutagenesis via chemical agents or ionizing radiation,¹¹⁸ it will require decades until such new techniques are able to fulfill those requirements. It is doubtful, however, that these requirements are strictly fixed to a clear cut-off date, eg in form of the Directive's adoption date, implying that any novel mutagenesis technique appearing or being mostly developed after the adoption date can never be covered by the mutagenesis exemption clause no matter how much time has passed since the Directive was adopted and for how long that new method has been in use after the Directive's adoption date. If this had been the will of the legislator, recital 17 could have explicitly stated that the Directive should not apply to those techniques which will appear or will be mostly developed after the date of adoption of the Directive.

Consequently, one may narrow the scope of the CJEU's judgment as regards its interpretation of the mutagenesis exemption clause. The reference to the adoption date of Directive 2001/18/EC (ie March 12, 2001) is, first, owed to the submissions of the referring French court, which explicitly asserted that the methods of directed mutagenesis, especially those called genome-editing, have been in use for breeding purposes only after the adoption of the Directive on March 12, 2001.¹¹⁹ Second, the adoption date might only serve as a starting point for assessing whether the qualitative ('conventional use'), quantitative ('in a number of applications'), and temporal ('long safety record') thresholds are met as regards such mutagenesis techniques which have appeared or been mostly developed after that date. Hence, the importance of the Directive's adoption date is that mutagenesis techniques having appeared or been mostly developed after that date need to be scrutinized carefully whether they fulfill the qualitative, quantitative, and temporal requirements implied in the mutagenesis exemption clause in light of recital 17 of the Directive. From this perspective, the judgement may be read as meaning that the aforementioned (qualitative, quantitative, and temporal) thresholds were (still) not met with regard to directed mutagenesis techniques, such as ODM or SDN mutagenesis techniques, at the point of time when the Court decided the case, ie on July 25, 2018.

117 Beck, *supra* note 64, at 253.

118 Which had been developed and used for breeding purposes as early as 1928; Bartsch et al., *supra* note 95, at 2.

119 *Confédération paysanne and Others*, *supra* note 3, at paras. 23 and 51.

As a consequence, translating this finding to the interpretation of the mutagenesis exemption of Directive 2009/41/EC, the decisive criterion is solely whether a technique has been used ‘conventionally . . . in a number of applications’ and has a ‘long safety record’. Whether the technique in question has appeared or has been mostly developed since the adoption date of Directive 2009/41/EC, ie May 6, 2009, is, therefore, irrelevant with regard to the problem of whether the qualitative (‘conventional use’), quantitative (‘in a number of applications’), and temporal (‘long safety record’) thresholds are met. The adoption date is only a point of reference for the question whether a mutagenesis technique was unknown to the legislator and, therefore, deserves closer scrutiny as to the implicit requirements of the mutagenesis exemption clause. From that point of view, it seems clear to us that, at least, CRISPR/Cas is a method of directed mutagenesis that can still not be considered to be covered by the mutagenesis exemption clause of 2009/41/EC.

*2. Self-cloning Exemption Clause, Art. 3 (1) (a), Annex II,
Part A (4) Directive 2009/41/EC*

Unlike Directive 2001/18/EC, Directive 2009/41/EC contains an exemption clause for micro-organisms obtained through so-called ‘self-cloning’. Whether certain applications of genome-editing can be considered to constitute self-cloning as understood by Annex II A (4) Directive 2009/41/EC can be set aside if the exemption does not apply to self-cloning via genome-editing in the first place.

The same arguments that speak against a permissive interpretation of the mutagenesis exemption can also be put forward here. Furthermore, there is no indication that the different exemptions stated in Annex II, Part A Directive 2009/41/EC should be interpreted differently since the risk-based interpretative approach applies to all exemptions laid down in Annex II, Part A Directive 2009/41/EC in the same manner. Therefore, the self-cloning exemption is to be interpreted as narrowly as the mutagenesis exemption.

III.D. Interim Conclusions

Genome-edited iPSCs are ‘GMMs’ within the meaning of the GMM definition laid down in Art. 2 (b) Directive 2009/41/EC. Hence, the provisions of Directive 2009/41/EC apply to the contained use of genome-edited iPSCs as long as the mutagenesis or self-cloning exemption clauses cannot be invoked. Whether these exemption clauses apply depends on whether the individual genome-editing technique used to modify the iPSCs (i) ‘has conventionally been used’ (qualitative threshold) (ii) in ‘a number of applications’ (quantitative threshold) and (iii) has ‘a long safety record’ (temporal threshold). It is, in our opinion, currently not possible to envisage that any genome-editing technique might fulfill these criteria. In any case, genome-editing via CRISPR/Cas does not meet the aforementioned three requirements implicit in the mutagenesis and self-cloning exemption clauses since this method of directed mutagenesis has been reported for the first time in 2012.

IV. IMPLICATIONS FOR DOMESTIC COURTS

So far, it has been shown to what extent the CJEU’s reasoning in case C-528/16 regarding the interpretation of the GMO definition and the mutagenesis exemption

clause of Directive 2001/18/EC can be translated to Directive 2009/41/EC and its interpretation as regards the GMM definition and the related mutagenesis (or self-cloning) exemption clause. However, what remains to be clarified are the implications of our findings for domestic courts. Are domestic courts legally bound to adopt the Court's interpretation of the GMO definition and the mutagenesis exemption clause of Directive 2001/18/EC when applying and construing the GMM definition and the related mutagenesis (or self-cloning) exemption clause of Directive 2009/41/EC?

The operative part of a preliminary ruling, such as the CJEU's ruling in case C-528/16, has a direct binding effect on the referring court and on national courts dealing with the same case in an appeal stage.¹²⁰ This binding effect encompasses the holding only. Albeit, the meaning and scope of the holding is, or may need to be, further clarified by the reasoning.¹²¹ Controversial is, however, the effect of a preliminary ruling on non-referring national courts and other national public authorities, ie its 'erga omnes' effect.¹²² This problem is irrelevant here, though, because even if all domestic courts of all EU Member States were directly legally bound by the Court's judgment in case C-528/16, the binding effect could not extend beyond what the Court had decided substantively ('ratione materiae'). Its holding is explicitly restricted to the interpretation of the Art. 2 (2), Art. 3 (1), Annex IA, IB (1) Directive 2001/18/EC.¹²³ In addition, the related reasoning¹²⁴ remains completely within the confines of Directive 2001/18/EC. In particular, even with regard to the contextual interpretation, the Court does not have recourse to any provision outside the Directive. The binding effect of the judgement as regards the interpretation of the GMO definition and the mutagenesis exemption clause of Directive 2001/18/EC does not directly extend to the interpretation of the GMM definition and the related mutagenesis (or self-cloning) exemption clause of Directive 2009/41/EC.

Accordingly, national courts are not bound by the CJEU's holding or rationale in case C-528/16 when it comes to the application and interpretation of national legislation implementing Directive 2009/41/EC. The remaining issue is whether a domestic court of last instance is obliged to refer the question of how to interpret the GMM definition or the mutagenesis or self-cloning exemption clause of Directive 2009/41/EC to the CJEU pursuant to Art. 267 (1)(b), (3) TFEU. Based on the CJEU decision in the CILFIT case, a national court of last instance may refrain from making a reference if the correct application of EU law is 'so obvious as to leave no scope for any reasonable doubt as to the manner in which the question raised is to be resolved'¹²⁵ (so-called 'acte clair' doctrine). As has been discussed intensely above,

120 Carl Otto Lenz, *The Role and Mechanism of the Preliminary Ruling Procedure*, 18 FORDHAM INT. LAW J. 388, at 403 (1994); ALAN DASHWOOD ET AL., WYATT AND DASHWOOD'S EUROPEAN UNION LAW, at 228 (6th ed., 2011); Morten Broberg & Niels Fenger, *Preliminary References*, in OXFORD PRINCIPLES OF EUROPEAN UNION LAW. THE EUROPEAN UNION LEGAL ORDER 981, at 1008 (Robert Schütze & Takis Tridimas eds., 2018); DAVID W. K. ANDERSON, REFERENCES TO THE EUROPEAN COURT, at 303 (1995).

121 Case 135/77, Robert Bosch GmbH v Hauptzollamt Hildesheim, 1978 ECLI:EU:C:1978:75, at para. 4.

122 On that debate see ROBERT SCHÜTZE, EUROPEAN UNION LAW, at 389 (2015); HENRY G. SCHERMERS & DENIS F. WAELEBROECK, JUDICIAL PROTECTION IN THE EUROPEAN UNION, at 305 (6th ed., 2001); ROBERT SCHÜTZE, AN INTRODUCTION TO EUROPEAN LAW, at 180 (2015); Anderson, *supra* note 121, at 308.

123 *Confédération paysanne and Others*, *supra* note 3, at no. 1 of the holding following para. 86.

124 *Id.* at paras. 26–54.

it can be reasonably assumed that the CJEU would interpret the GMM definition as well as the mutagenesis or self-cloning exemption clause laid down in Directive 2009/41/EC in a similar or identical way as done in case C-528/19. It can be inferred from our in-depth analysis above that such an outcome is not set in stone, though, ie different legal interpretative approaches might be justifiable as well. Therefore, the CILFIT rule, or ‘acte clair’ doctrine, is not applicable here. Consequently, a domestic court of last instance would be obliged to refer the question of how to interpret the GMM definition or the mutagenesis and self-cloning exemption clauses laid down in Directive 2009/41/EC to the CJEU.

V. CONCLUSIONS

The CJEU’s interpretation of the GMO definition in case C-528/16 provided clarity far beyond the scope of Directive 2001/18/EC. On the basis of our analysis, we are confident that the CJEU’s interpretation and underlying reasoning can be extended to the GMM definition of Directive 2009/41/EC.

The situation is slightly different with regard to the mutagenesis (and self-cloning) exemption clauses. Even though wording and structure of the exemption clauses in Directive 2001/18/EC and Directive 2009/41/EC are virtually identical, there is one important difference which is recital 17 of Directive 2001/18/EC which has no equivalent in Directive 2009/41/EC. Recital 17, however, is an important cornerstone, if not ‘the’ cornerstone, of the Court’s reasoning as regards the interpretation of the mutagenesis exemption clause of Directive 2001/18/EC. Hence, it required lengthy argumentation to establish that also the Court’s interpretation of the mutagenesis exemption clause of Directive 2001/18/EC can be translated to the understanding of the mutagenesis (and self-cloning) exemption clause of Directive 2009/41/EC. Therefore, we assume that the CJEU would—if asked—arrive at the same conclusions as regards the interpretation of the exemption clause of Directive 2009/41/EC even if the reasoning underlying the judgement in case C-528/16 would have to be slightly adapted to fit Directive 2009/41/EC.¹²⁶

Nevertheless, in the end, the regulatory status quo of genome-edited GMMs, especially of genome-edited human iPSCs, remains characterized by legal uncertainty in regard to the requirements implied in the mutagenesis (and self-cloning) exemption clauses of both Directive 2009/41/EC and Directive 2001/18/EC. This is so because the Court has not pronounced on the meaning of ‘conventional use’, ‘a number of applications’, and ‘a long safety record’. Whether these qualitative, quantitative, and temporal thresholds are met has to be decided case-by-case depending on the individual genome-editing technique used to genetically modify the relevant (micro-)organism. For sure, GMOs or GMMs, in particular genome-edited human

125 C-283/81, *Srl CILFIT and Lanificio di Gavardo SpA v. Ministry of Health*, 1982 ECLI:EU:C:1982:335, at para. 16.

126 Similar opinion Tade Matthias Spranger, *Case C-528/16: Questions Raised by the ECJ’s Judgement on Gene Editing Technology*, 1 INT. CHEMICAL REGULATORY LAW REV. 173, at 176 (2018); Tade Matthias Spranger, *Memorandum on the Question of the Applicability of the Statements of the European Court of Justice in case C-528/16 to the Area of Regulation of Directive 2009/41/EC on the Contained Use of Genetically Modified Micro-Organisms* (2019).

iPSCs, obtained through CRISPR/Cas cannot be considered exempted for the time being.

Accordingly, for purposes of legal certainty, further interpretative clarification by the CJEU would be helpful. The most desirable way to provide legal certainty would be, however, to revise both Directive 2009/41/EC and Directive 2001/18/EC by amending the GMO and GMM definitions [ie the ‘front doors’ admitting (micro-)organisms to the legal frameworks] or the exemption clauses (ie the ‘back doors’ allowing for the escape from the legal frameworks). In the course of such a revision process it would be, of course, necessary to debate whether the underlying risk assumptions regarding genome-editing are sensible and scientifically sound at all. From our point of view, and in line with claims and statements made by scientists,¹²⁷ the GMO and GMM definitions or the exemption clauses should be amended so as to exclude genome-edited (micro-)organisms from the scope of application of the legal frameworks applying to GMOs and GMMs, respectively, at least as far as no ‘transgenes’ are inserted into the genome of the recipient (micro-)organisms or the genetic modification could have occurred in nature or through conventional breeding techniques as well.

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127 Dennis Eriksson et al., *A Welcome Proposal to Amend the GMO Legislation of the EU*, 36 *TRENDS BIOTECHNOL.* 1100, at 1101 (2018); Josep M. Casacuberta & Pere Puigdomènech, *Proportionate and Scientifically Sound Risk Assessment of Gene-Edited Plants*, 19 *EMBO REP.* (2018); Kai P. Purnhagen et al., *EU Court Casts New Plant Breeding Techniques into Regulatory Limbo*, 36 *NAT. BIOTECHNOL.* 799 (2018); Wasmer, *supra* note 7, at 9; Charlotta Zetterberg & Karin Edvardsson Björnberg, *Time for a New EU Regulatory Framework for GM Crops?*, 30 *J. AGRIC. ENVIRON. ETHICS* 325, at 341 (2017); Nationale Akademie der Wissenschaften Leopoldina, *Towards a Scientifically Justified, Differentiated Regulation of Genome Edited Plants in the EU*, at 74 (2019).