Position paper on the amendment of the European GMO legal framework for microorganisms

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Industrial Bioeconomy Dialogue Platform: Who we are

The Federal Ministry for Economic Affairs and Energy's "Industrial Bioeconomy" dialogue platform is an independent network of 300 experts from industry, science and the public sector. It actively shapes the further development of the industrial bioeconomy in Germany and provides sound, practical expertise to promote innovative solutions for a sustainable, competitive and bio-based industry. The platform systematically contributes its views to political decision-making processes – for example through statements, position papers and consultations – and facilitates targeted exchange between industry, science and politics. In this way, it supports policymakers in developing industry-relevant strategies and technological change.

1. Summary

The current EU regulations governing genetically modified organisms (GMOs) and, in particular, genetically modified microorganisms (GMMs) pose major challenges for companies seeking approval for innovative products and production processes. New genomic techniques (NGTs) in particular, such as the Nobel Prize-winning CRISPR/Cas technology, offer enormous potential for biotechnology as a key technology for a future-oriented, climate-neutral and sustainable economy. This position paper describes an evidence- and knowledge-based proposal for redesigning the European GMO legal framework for microorganisms. This proposal involves focusing on the assessment of a commercial product as such (= product-based) instead of the previous focus on the manufacturing process (= process-based). The central demand is a shift away from the previous process-based approach to a product-based GMO legal framework (see Chapter 5). The type of genetic modification determines the classification of a (GM) microorganism into one of three categories. The corresponding categorisation of the microorganism and its intended use (contained use or placing on the market) determine the scope/effort of registration, the authorisation requirements and the labelling obligation.

The BMWE's Industrial Bioeconomy Dialogue Platform supports the position paper presented here and emphasises the urgency of its implementation to secure the competitiveness of the European biotechnology industry.

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2. Introduction and objectives

The use of genetically modified microorganisms offers many advantages for the industrial bioeconomy but faces regulatory challenges.

The European Green Deal and the Clean Industrial Deal have set ambitious targets for climate, the circular economy and a sustainable food system. A range of solutions is needed to achieve these targets and create a climate-neutral and sustainable European economy. One of these is the use of key technologies such as biotechnology.

Industrial biotechnology is a central pillar of innovation in Europe. It is essential for a functioning bioeconomy in which renewable resources, residual materials and CO_2 are used efficiently and sustainably. Industrial biotechnology provides both living microorganisms and fermentation products. These are used in areas such as food and feed, agriculture, detergents, paper and pulp, textiles, fuels, bioenergy and specialty chemicals.

There are examples of products in which the living microorganism itself is marketed as a product in many areas: probiotics, beer and wine yeasts, dairy cultures, microorganisms for biological remediation, bacteria for promoting plant growth and biological pest control, and microbes in body cleansing, cosmetic and hygiene products.

In addition, there are numerous fermentation products that are produced with the help of microorganisms in a closed system. In these cases, the organism itself is not part of the product. These include, for example, amino acids, enzymes, vitamins, colourings, omega-3 fatty acids, low-calorie sweeteners, flavourings or flavour enhancers, human milk oligosaccharides and vegan alternatives to milk and meat products.

Some aspects of innovation in industrial biotechnology are based on the genetic improvement of microorganisms that are used as products (= target use "placing on the market") or as production organisms for fermentation products (= target use "contained use"). This is achieved using safe and robust techniques, tools and methods that are constantly evolving.

The use of optimised, genetically modified microorganisms offers industrial biotechnology many efficiency and sustainability advantages, such as:

- Increased product and process safety through the elimination of potentially safety-relevant genes
- Improvements in nutrient utilisation,
- Increased resource efficiency, and
- Reduction of the ecological footprint.

Access to state-of-the-art, efficient, precise and safe genetic engineering tools (such as genome editing techniques) is crucial for research and development in the EU, particularly in the field of industrial biotechnology. The use of these methods significantly accelerates the product development process. In order to make optimal use of these tools, a scientifically sound, proportionate and reliable regulatory approach for current and future biotechnological innovations is urgently needed. This is essential if the EU wants to remain competitive and retain its existing innovation potential.

Looking to the future, genetic engineering and industrial biotechnology will play a decisive role in overcoming the socio-economic and ecological challenges facing our planet. They are paving the way for the transition from a largely linear fossil-based economy to a circular bioeconomy. This means minimising raw material consumption and waste generation and ensuring the future viability of the global economy.

Genetic engineering and industrial biotechnology have outstanding potential[1] to make a significant contribution to a more sustainable future. With their support, we can achieve our ambitious goals in combating climate change, biodiversity loss and increasing food security. It is essential that the regulatory framework and constructive public debate support innovation in this area.

One of the key regulatory challenges at present is the process-based EU GMO legal framework, which was developed in the 1980s and 1990s. Technological developments that have emerged since then are not taken into account. Any newly developed (genetic engineering) methodology would have required an amendment to the process-based legislation. Unfortunately, such amendments have never been made, creating major challenges for the industry due to regulatory and economic uncertainty.

Thanks to technological progress, it is now possible to optimise organisms in such a targeted manner that it is not possible to clearly determine from the organism alone whether it was created naturally/conventionally or through genetic engineering. As a result, different approvals are currently required for the same products (see example in the box below).

Case study on the issue of process-based regulation: A probiotic product is to be approved for use as a feed additive.

A) The product contains as an active component a microorganism modified by **radiation-induced mutagenesis**, which exhibits several randomly introduced mutations. This requires product authorisation in accordance with Regulation (EC) No 1831/ 2003[2] on additives for use in animal nutrition.

B) The identical probiotic product containing the microorganism with exactly the same modifications* ,but which have been introduced by **targeted mutagenesis** using controlled and safe biotechnological methods, requires, in addition to product authorisation as a feed additive in accordance with Regulation (EC) 1831/2003, authorisation as a genetically modified feed in accordance with Regulation (EC) 1829/2003[3] .In addition, labelling as a GMO is required, even though the control authorities cannot detect the technique used to modify the microorganism in the probiotic product. Furthermore, GMO registration is expensive, costing millions, and takes more than five years, which is not justifiable from an economic point of view, especially for niche products such as feed additives.

* Verified by whole genome sequencing

EU legislative proposal for NGT plants

The EU legislative proposal of July 2023, which is currently in the works, deals with plants developed using certain new genomic techniques (NGT), such as targeted mutagenesis and cisgenesis, including intragenesis. This proposal is an encouraging sign and represents an important first step towards addressing the issue of different regulations and labelling for identical products, at least in the plant sector (see box below for further details). However, microorganisms have not yet been included in this legislative proposal.

The original **EU legislative proposal for NGT plants** from 2023 includes the creation of two different pathways for placing NGT plants on the market. **Category 1** includes NGT plants that contain changes that occur naturally or are produced by conventional breeding methods. This includes their progeny obtained by conventional breeding of such NGT plants. In the 2023 proposal, an NGT plant is considered "equivalent" to a conventional plant and thus a Category 1 plant if it differs from the recipient/parental plant by no more than 20 genetic modifications (for details, see *New techniques in biotechnology - European Commission)*. Category 1 NGT plants would be exempt from the applicable EU GMO regulations. The extent to which they would need to be labelled is currently being discussed in the EU trilogue. For all other genome-edited plants, NGT plants in **category 2**, with greater modifications and genetic material from other species, the GMO legislation would apply (including a risk assessment and authorisation prior to placing on the market). These would then also be labelled as GMOs accordingly.

However, the proposed legislation for NGT plants remains stuck in a process-centred approach, as it only regulates certain NGTs (targeted mutagenesis and cisgenesis, including intragenesis). Newly emerging techniques that would also meet the criteria for Category 1 NGT plants would require new legislation.

In view of the market entry barriers presented above due to the current EU GMO legal framework, we hereby propose a shift away from the current process-based approach to the assessment of GMOs towards a product-based approach, with a special focus on microorganisms. This position paper provides a concrete proposal for how an EU GMO legal framework for microorganisms could be designed. We consider microorganisms that are directly the product (= target use "placing on the market") or are used for the production of fermentation products without themselves being part of the product (= target use "contained use").

3. International framework conditions and current EU GMO legislation

This chapter introduces the international framework and current EU GMO legislation and provides an overview of sectoral legislation.

In the context of the discussion on product-based regulation of genetically modified microorganisms (GMMs) at EU level, the analysis of existing international and European legislative architecture is central. The focus here is on three sets of regulations in particular, which provide basic definitions for "(micro-)organism", "genetically modified" and the areas of application "deliberate release", "placing on the market" and "contained use". These regulatory frameworks serve as reference points in international agreements as well as in sectoral EU legislation and directives (e.g. Regulation (EC) 1829/2003[3] on genetically modified food and feed; Regulation (EC) 1831/2003[2] on additives for use in animal nutrition; EFSA guideline on the characterisation of microorganisms used as feed additives or production organisms).

3.1. Cartagena Protocol on Biosafety (2003)

The Cartagena Protocol[4] is a binding international agreement under the umbrella of the Convention on Biological Diversity (CBD). It regulates the transboundary movement of living (genetically) modified organisms (LMOs) with the aim of protecting biological diversity and human health from potential risks posed by LMOs. The EU is a party to the Protocol and has incorporated key definitions and principles – particularly the precautionary approach – into its legal system.

3.2. Directive 2001/18/EC – Deliberate release of GMOs into the environment

Directive 2001/18/EC[5] provides the authoritative definition of "genetically modified organisms" (GMOs) at EU level. Regulatory classification is based on a process-based approach: it is not the end product that is decisive, but the technique used to modify the genetic material. The Directive lists:

(a) techniques that result in a GMO,
(b) techniques that do not result in a GMO,
(c) genetic modification techniques that result in organisms that are exempt from the Directive.

These definitions have horizontal effect, i.e. they also influence other sector-specific regulations in areas such as agriculture, the environment and food safety.

3.3. Directive 2009/41/EC – Contained use of genetically modified microorganisms

Directive 2009/41/ EC[6] regulates the handling of GMMs in contained systems (e.g. laboratories, industrial bioreactors). This is also a process-based approach. However, the Directive contains different lists of exempted techniques compared to Directive 2001/18/EC[5]. Of particular note here is self-cloning, a very important technique for increasing the number of copies of genes, among other things. Self-cloning is designated as an exempted GMO technique in Directive 2009/41/EC, but according to Directive 2001/18/EC it is a GMO technique (see Table 1).

3.4. Overview of existing sectoral legislation

The following is a list of examples of sectoral legislation in which the risk assessment of microorganisms is part of the product authorisation process:

- Feed additives in accordance with Regulation (EC) No 1831/2003[2];
- Food enzymes according to Regulation (EC) 1332/2008[7];
- Food additives according to Regulation (EC) 1333/2008[8];
- Flavourings or food ingredients with flavouring properties according to Regulation (EC) 1334/2008[9];
- Novel foods according to Regulation (EC) 2015/2283[10];
- Plant protection products according to Regulation (EC) 1107/2009[11];
- Biocidal products pursuant to Regulation (EC) No 528/2012[12].

In cases where the genetically modified microorganism is present in a viable form in the product, the product must also be authorised as a GMO under Regulation (EC) No 1829/2003[3] if the product is to be placed on the market as food or feed. If the product is to be used in other areas of application, Directive 2001/18/EC[5] applies in these cases. An exception to this procedure are so-called novel foods. These may not be GMOs; i.e. if they are GMOs, they must be authorised solely under Regulation (EC) 1829/2003[3] and must then be labelled as GM foods.

3.5. Summary of the "status quo" of EU GMO regulations for microorganisms

The authorisation requirements for microorganisms as products and as production strains differ depending on their origin or production method, as explained below.

Wild-type strains and non-GMO strains (in accordance with Directive 2001/18/EC[5] Annex I A Part 2 and Directive 2009/41/EC[6] Annex I Part B) are not covered by EU GMO regulations (Table 1, lines 1 and 2).

GMO strains in accordance with Directive 2001/18/EC Annex I A Part 1 and Directive 2009/41/EC Annex I Part A are subject to EU GMO authorisation and labelling requirements if the microorganism is contained in the commercial product. There is an exemption from the GMO authorisation and labelling requirements for GMO production strains, provided that they are not contained in the commercial product (Table 1, row 3). Authorisation of the genetic engineering facility is required in order to use GMO strains in a closed system.

Strains that are defined as **GMO**s but are **exempted** from this requirement under Annex I B of **Directive 2001/18/EC** are not subject to GMO authorisation and labelling requirements (Table 1, row 4).

According to **Directive 2009/41/EC** Annex II Part A, strains defined as **GMO**s and **exempted** from the Directive are not subject to GMO authorisation and labelling requirements as long as they are not contained in the commercial product. As soon as the strain is contained in the product, it must be checked whether the procedure listed in Annex II, Part A of Directive 2009/41/EC is also listed in Annex I B of Directive 2001/18/EC. Strains that have been modified, for example, by self-cloning are exempt from the regulatory requirements of Directive 2009/41/EC, but not from those of Directive 2001/18/EC. This means that a strain generated by **self-cloning** that is contained in a commercial product is subject to GMO authorisation and labelling requirements (Table 1, row 5).

*Table 1: "Status quo" of EU GMO regulations for microorganisms. *MO = microorganism. GMO authorisation = approval for placing on the market in accordance with Regulation (EC) 1829/2003 or Directive 2001/18/EC and labelling requirement. Approval of the genetic engineering facility is required for the use of GMO strains in a closed system.*

Type of authorisation	Sector-specific authorisation		GMO authorisation	
MO* are:	Product	Production strain	Product	Production strain
Wild-type strains: unchanged	Yes, if required	Yes, within the scope of product authorisation, if required	No	No
Non-GMO strains according to 2001/18/EC[5] Annex I A Part 2 and 2009/41/EC[6] Annex I Part B	Yes, if required	Yes, within the scope of product authorisation, if required	No	No

Type of authorisation	Sector-specific authorisation		GMO authorisation	
MO* are:	Product	Production strain	Product	Production strain
GMO strains according to 2001/18/EC[5] Annex I A Parts 1 and 2009/41/EC[6] Annex I Part A	Yes, if required	Yes, within the scope of product authorisation, if required	Yes	No
GMO strains **exempted** under Annex I B of **2001/18/EC**[5]	Yes, if required	Yes, within the scope of product authorisation, if required	No	No
GMO strains **exempted** under Annex II, Part A of **2009/41/EC**[6]	Yes, if required	Yes, within the scope of product authorisation, if required	Yes, in the case of self-cloning	No

Distinction between sectoral and GMO authorisation

In the context of GMO authorisation, an environmental risk assessment (ERA) is required in comparison to sectoral product authorisation, e.g. as a feed or food additive. The general principles for an ERA are:

- Identification of GMO traits that may have harmful effects;
- Assessment of the possible consequences of any adverse effects;
- Assessment of the probability of a potential harmful effect occurring;
- Estimation of the risk posed by each identified characteristic;
- Application of strategies/measures for risks arising from the deliberate release/marketing of the GMO; and
- Determination of the overall risk posed by the GMO.

In this context, the development of a detection method by the company in collaboration with the JRC (Joint Research Centre of the European Commission) in a multi-year and cost-intensive process for tracking/monitoring the GMO and quantifying it is of central importance in the authorisation process.

4. Definitions according to existing EU law

The following chapter defines the basic terms according to existing EU directives, which are also of central importance for the proposed amendment described in Chapter 5.

In addition, we also provide a biological definition of organism to focus on the characteristics of life that must be fulfilled to be considered an organism. At the end of this chapter, Table 2 shows a comparison of the basic definitions in Directive 2001/18/EC on the deliberate release of GMOs into the environment and Directive 2009/41/EC on the contained use of genetically modified microorganisms.

4.1. Organism

Directive 2001/18/EC (Article 2, point 1)[5] on the deliberate release into the environment of genetically modified organisms: "organism" means any biological entity capable of replication or of transferring genetic material.

4.2. Organism – biological definition[13]

An organism is a single, self-contained, living system that fulfils the characteristics of life. These include:

- Metabolism
- Growth
- Irritability (reaction to environmental stimuli)
- Reproduction
- Self-organisation (building and maintaining complex structures)
- Evolutionary adaptation

4.3. Microorganism

In accordance with Directive 2009/41/EC[6] (Article 2; letter a) on the contained use of genetically modified microorganisms: 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.

4.4. Genetically modified organism (GMO)

According to Directive 2001/18/EC (Article 2, point 2)[5], a GMO is an organism, with the exception of human beings, in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. For the purposes of this definition, the following applies:

a) Genetic modification is achieved at least by the use of the techniques listed in Annex I A, Part 1:

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

2. **Techniques involving the direct introduction into an organism** of heritable material prepared outside the organism including micro-injection, macro-injection and micro-encapsulation;
3. **Cell fusion** (including protoplast fusion) or hybridisation techniques where living 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.

b) The techniques listed in Annex I A, Part 2, are not considered to result in genetic modification:

Techniques within the meaning of Article 2 Number 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 in Annex I B:

1. *in vitro* fertilisation,
2. natural processes such as conjugation, transduction, transformation,
3. polyploidy induction.

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

1. mutagenesis,
2. cell fusion (including protoplast fusion) of plant cells of organisms which can exchange genetic material through traditional breeding techniques.

4.5. Genetically modified microorganism (GMM)

According to Directive 2009/41/EC[6] (Article 2 (b)), a GMM is a microorganism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination. For the purposes of this definition, the following applies:

a) Annex I, Part A: Genetic modification techniques within the meaning of Article 2(b)(i) include, 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 a micro-organism of heritable material prepared outside the micro-organism, including micro-injection, macro-injection and micro-encapsulation.
3. Cell fusion or hybridisation techniques where living 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.

b) The processes listed in Annex I, Part B are not considered to result in genetic modification.

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

1. *In vitro* fertilisation.
2. Natural processes such as conjugation, transduction, transformation.
3. Polyploidy induction.

c) Annex II, Part A - Techniques or methods of genetic modification yielding microorganisms to be excluded from the 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;
2. Cell fusion (including protoplast fusion) of prokaryotic species that exchange genetic material by known physiological processes;
3. Cell fusion (including protoplast fusion) of cells of any eukaryotic species, including the production of hybridomas and plant cell fusions;
4. Self-cloning consisting in the removal of nucleic acid sequences from a cell of an organism which may or may not be followed by reinsertion of all or part of that nucleic acid (or a synthetic equivalent), with or without prior enzymic or mechanic steps, into cells of the same species or into cells of phylogenetically closely related species which can exchange genetic material by natural physiological processes where the resulting microorganism is unlikely to cause disease to humans, animals or plants. Self-cloning may include the use of recombinant vectors with an extended history of safe use in the particular microorganism.

4.6. Deliberate release

According to Directive 2001/18/EC[5] (Article 2, point 3), deliberate release means any intentional introduction into the environment of a GMO or a combination of GMOs for which no specific containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment.

4.7. Placing on the market

According to Directive 2001/18/EC[5] (Article 2, point 4), placing on the market means making available to third parties, whether in return for payment or free of charge.

The following operations shall not regarded as placing on the market:

a) Making available genetically modified microorganisms for activities regulated by Council Directive 90/219/EEC[14] of 23 April 1990 on the contained use of genetically modified microorganisms, including culture collections;

b) Making available GMOs other than microorganisms referred to in (a), to be used exclusively for activities where appropriate stringent containment measures are used to limit their contact with and to provide a high level of safety for the general population and the environment; the measures should be based on the same principles of containment as laid down in Directive 90/219/EEC;

c) Making available GMOs to be used exclusively for deliberate releases complying with the requirements laid down in Part B of this Directive.

4.8. Contained use

According to Directive 2009/41/EC[6] (Article 2(c)), contained use means any activity in which microorganisms are genetically modified or in which such GMMs are cultured, stored, transported, destroyed, disposed of or used in any other way, and for which specific containment measures are used to limit their contact with, and to provide high level of safety for, the general population and the environment.

Table 2: Comparison of the definitions of GMOs and GMMs (according to EU Directives 2001/18/EC[5] and 2009/41/EC[6])

	GMO (genetically modified organism)	GMM (genetically modified microorganism)
Legal basis	Directive 2001/18/EC[5] on the deliberate release into the environment of genetically modified organisms	Directive 2009/41/EC[6] on the contained use of genetically modified microorganisms
Definition Organism / microorganism	Any biological entity capable of replication or transferring genetic material.	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.
Definition of GMO / GVM	Organism, with the exception of human beings, in which genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.	Microorganism in which the genetic material has been altered in a way that does not occur naturally by mating and/or natural recombination.

	GMO (genetically modified organism)	GMM (genetically modified microorganism)
Methods leading to a GMO / GMM	• Recombinant nucleic acid techniques • Processes in which genetic material prepared outside the organism is introduced directly into an organism, including micro-injection, macro-injection and micro-encapsulation; • Cell fusion or hybridisation techniques	• Recombinant nucleic acid techniques • Processes in which genetic material produced outside the microorganism is introduced directly into the microorganism, including micro-injection, macro-injection and micro-encapsulation. • Cell fusion or hybridisation techniques
Methods that result in a non-GMO / non-GMM	• *In vitro* fertilisation • Natural processes such as conjugation, transduction, transformation • Polyploidy induction	• *In vitro* fertilisation • Natural processes such as conjugation, transduction, transformation • Polyploidy induction
Methods that lead to a GMO/GMV but are excluded from the Directive	• Mutagenesis • Cell fusion of plant cells	• Mutagenesis • Cell fusion of prokaryotic species • Cell fusion of eukaryotic species • Self-cloning

5. Proposal for product-based EU legislation on microorganisms

In the following, we use case studies to illustrate the urgency of adapting the current process-based legal framework and explain our proposal for a product-based approach for microorganisms.

The existing EU GMO legal framework is process-based. In an age of technological progress, where the boundaries between conventional and genetic engineering methods are becoming increasingly blurred and it is difficult or impossible to verify the process method used in the end product, this leads to major problems. These include regulatory and economic uncertainty for industry and authorities, as well as potentially different approvals for the same products. This means that a product that contains a genetically identical GMM or has been produced using it – but with different techniques – is subject to different regulatory obligations. In addition, different labelling requirements apply to GMOs/GMMs (see case study in Chapter 2). However, the modification method can no longer be verified in the finished product.

The current EU legal framework for GMOs was developed in the 1980s and 1990s (updated in 2001 and 2009) and does not take into account the technological developments that have emerged since then (both in terms of genetic engineering techniques and analytical methods, e.g. whole genome sequencing). However, it would be essential to adapt process-based legislation whenever a new

methodology emerges. In view of the current outdated process-centred EU GMO legal framework, we propose a shift towards a product-based approach. The case studies summarised in Table 3, which are explained in detail in Chapter 6, illustrate the urgent need for a fundamental revision of GMO legislation in the EU.

For plants, a proposal is already in the works in the form of the draft NGT Regulation, which attempts to partially resolve the fundamental problem of differing regulations and labelling for identical products. For microorganisms, which are not covered by the current legislative proposal for plants, we believe that a gradual categorisation system (whether GMM or non-GMM) should be considered (see 5.1). This would allow the scope/effort of registration and the approval requirements to be brought into proportion with the type of genetic modification.

Risk-based safety assessment

It is important to emphasise that it is the fundamental responsibility of the company to prove beyond doubt that a microorganism is safe for humans, animals and the environment before marketing it. Regardless of the required regulatory approval process, it goes without saying that this thorough, scientific and risk-based safety assessment must be based on the latest scientific standards and regulations. In addition, existing risk class classification requirements are complied with in order to ensure unrestricted safety. Almost without exception, microbial strains of risk class 1 (the lowest possible risk level) are used. Occasionally, there are exceptions with regard to the use of microbial strains in risk class 2. As long as the questionable property/gene sequence that causes classification in risk class 2 is not present in the strain, it should not be excluded from possible use as a production strain and/or marketing as a product.

Table 3: Case studies illustrating the need for a fundamental revision of EU GMO legislation.

Chap.	Product	Intended use	Problem	Solution
5.1	Biomass-containing amino acid as feed additive	GMM as production strain	No economically viable and competitive marketing opportunities in the EU	Clarification of the scope of Regulation (EC) No 1829/2003[3] and the terminology of deliberate release/placing on the market in comparison to the contained use of microbial production strains
5.2	Amino acid, vitamin, enzyme as feed additive	GMM as production strain	Changes to the production strain (necessary to remain competitive) may require a new product authorisation	Fundamental revision of Directive 2009/41/EC[6]: Shift from a process-centred to a product-centred approach

Chap.	Product	Intended use	Problem	Solution
5.3	Probiotic as feed additive	Placing the GMM on the market	Microorganism excluded from authorisation due to existing resistance to antibiotics; elimination of undesirable characteristics (in this case, resistance) through targeted mutagenesis techniques not possible due to regulatory restrictions	Fundamental revision of Directive 2001/18/EC[5]: Shift from a process-centred to a product-centred approach
5.4	Yeast culture for beverage production	Placing the GMM on the market	Due to the process-oriented GMO regulation and the resulting GMO regulatory requirements and labelling, there is a risk of lacking customer acceptance	Fundamental revision of Directive 2001/18/EC[5]: Shift from a process-centred to a product-centred approach
5.5	Food cultures	Placing GMOs on the market	Legal uncertainty for organisms whose origin cannot be clearly verified based on the organism itself.	Fundamental revision of Directive 2001/18/EC[5]: Shift from a process-centred to a product-centred approach

5.1. Proposed categorisation of microorganisms as products or production strains

The categorisation of the microorganism (based on the type of genetic modification) and the intended use of the product (placing on the market or contained use) determine the scope/effort of registration, the authorisation requirements and the labelling requirements. The following categories are proposed (see Table 4).

Category 0

According to our proposal, category 0 microorganisms are **wild-type strains and strains mutated using conventional methods**. Conventional methods are procedures listed in the current EU GMO legal framework that do not result in GMOs, as well as genetic modification techniques (e.g. mutagenesis through chemicals, radiation) that do result in GMOs, which are to be excluded from the directives. WT strains and strains mutated by conventional methods should not be subject to GMO legislation or GMO labelling, as is already the case in the current legal framework. For Category 0 microorganisms, depending on the intended use, product authorisation may be required, taking into account sectoral legislation.

For microorganisms used as production organisms, if a (strain-specific) product authorisation already exists, it should be possible to introduce changes to the strain corresponding to category 0 (e.g. mutagenesis by chemicals, radiation), which are documented and verified by an independent certifier (e.g. FAMI-QS in the case of feed additives). This documentation is a summary of a risk assessment and impact assessment of the intended strain modification, addressing the following points and including relevant documents and controls (e.g. summarised laboratory results):

- Detailed description of the strain modification (including statements on the effects on the safety profile and metabolism of the microorganism),
- Effects on the production process and the end product (specification, composition, purity, physical-chemical properties, hygiene status),
- Explanations of possible risks to humans (consumers, users, employees), the environment and, where applicable, depending on the area of application, target animals and the food chain.

The categorisation of the microorganism of the old and new production strain, i.e. category 0, remains unchanged. The issue of the requirement for renewed EU approval of a fermentation product in the event of changes to the production strain is a specific problem of EU feed legislation. Other legislation, e.g. in the food sector, already provides for the possibility of adapting the relevant EU market authorisation through a shortened process.

Category 1 (cisgenetics)

Category 1 includes genetically modified microbial strains that are free of (functional) foreign DNA. Examples of such modifications are point mutations, an increase in the number of gene copies or a promoter exchange.

Methods that lead to the production of such modified strains include self-cloning and the exchange of genetic information between closely related taxonomic units (for which such an exchange of genetic information is a documented, normal phenomenon) and the targeted introduction of nucleotide substitutions. Since it is difficult or impossible to detect the genetic modification method used in the end product, these strains should be regulated in the same way as Category 0 strains. This means that only product authorisation is required, taking into account sectoral legislation. However, in order to ensure transparency for the end customer/consumer, it is proposed that the specific modification introduced be reported to an EU Member

State and entered in a register, similar to the procedure described in the NGT proposal for category 1. A registry office or authority responsible for this in Germany should be designated as part of the subsequent implementation of corresponding legislation. With regard to data collection, the databases of the Central Committee on Biological Safety (ZKBS) could serve as a guide. However, this additional administrative effort should only be relevant for category 1 microorganisms that are placed on the market as products, i.e. the living organism is part of the commercial product.

Microorganisms whose risk assessment is already part of sectoral product approval should be exempt from notification or register entry (see example in box).

Case study for the exemption from notification or register entry of a Category 1 GMM

Five point mutations were introduced into a probiotic strain for use as a feed additive by means of targeted mutagenesis. This means that it falls into category 1 (cisgenetics) according to the new categorisation proposal. The strain is the commercial product. Sectoral product authorisation as a feed additive requires compliance with Regulation (EC) 1831/2003[2]. As part of this authorisation, the EFSA conducts a comprehensive risk assessment of the strain. The strain is described in detail as part of the authorisation, including the genetic modifications. Since the genetic modifications have already been described as part of the sectoral product authorisation, a register entry is not required.

For microorganisms used as production organisms, it should be possible to introduce changes to the strain in the case of an existing sectoral product authorisation. The documentation (scope of the data package identical to category 0; see above) should be reviewed by an independent certifier. The category of the old and new production strains is limited to category 0 and/or 1.

Category 2 (transgenics)

Category 2 includes genetically modified microbial strains in which heterologous sequences (= foreign DNA) have been introduced (transgenics) or heterologous sequences have been generated, but also microorganisms that have been designed from scratch (synthetic biology). The introduction of foreign DNA means the introduction of heterologous genes, i.e. genetic information originating from another species that is not closely related. With regard to the necessary approval requirements, the intended use of the product (placing on the market or contained use) should be decisive. As long as the living microorganism is not part of the product, i.e. it has been removed or inactivated after fermentation, only product authorisation is required, taking into account sectoral legislation that already includes risk assessment of the strain. No additional GMO regulation is required, i.e. no authorisation under Regulation (EC) No 1829/2003[3] in the case of food and feed, or Directive 2001/18/EC[5] .

In the case of existing sectoral product authorisations and the contained use of the GMM, approval of any changes to the strain in the form of notifications should be considered. The notification procedure should be entrusted to the authority responsible for sectoral product authorisation, e.g. for feed and food, the European Commission and the European Food Safety Authority (EFSA). The relevant dossier shall contain a detailed description of the changes to the strain, describe the effects on the production process and the final product, and provide explanations of possible risks to humans, animals and the environment.

A product containing a microorganism in the category 2 proposed by us and intended to be placed on the

market requires product authorisation in accordance with sectoral legislation and GMO regulations, as well as appropriate GMO labelling.

5.2. Decision-making aids for classifying microorganisms into the three categories

Table 4 provides a comparative overview of the three categories described in Chapter 5.1 for the case of placing on the market and contained use. The overview also describes the final labelling requirements for commercial products.

Figure 1 summarises our proposal for a gradual categorisation system. The decision tree facilitates the classification of a microorganism (as a production strain or end product) into the three categories described in Chapter 5.1 based on its genetic nature.

Table 4: Proposal for a gradual categorisation system for microorganisms. *(Regulation according to GMO means authorisation under Regulation (EC) 1829/2003 or Directive 2001/18/EC and labelling requirement).*

	Category 0	Category 1	Category 2
General description	Wild-type strain or microbial strain mutated using conventional methods (excluded from GMO legislation)	Genetically modified microbial strain without (functional) foreign DNA (**cisgenetics**)	Genetically modified microbial strain in which heterologous sequences have been introduced or reconstructed (**transgenics**)
Approval in the case of placing on the market (microorganism is part of the product)	Product authorisation in accordance with sectoral legislation; **no** regulation under GMO	Product authorisation taking into account sectoral legislation; **no** regulation under GMO; notification to an EU Member State and, if necessary, entry in a register (similar to the procedure described in the NGT proposal for category 1)	Product approval taking into account sectoral legal provisions; **regulation according to GMO**

	Category 0	Category 1	Category 2
Approval for contained use of the strain (microorganism is a production strain)	As above; if product authorisation has already been granted, review of documentation on changes to the strain by an independent certifier	As above; if product authorisation has already been granted, review of documentation on changes to the strain by an independent certifier	Product authorisation taking into account sectoral legal requirements; no regulation under GMO due to the absence of GMO in the product when used in a closed system; if product authorisation has already been granted, approval of changes to the strain through notification procedure
Labelling of the final product	No GMO labelling	No GMO labelling	In the case of placing the organism on the market GMO labelling

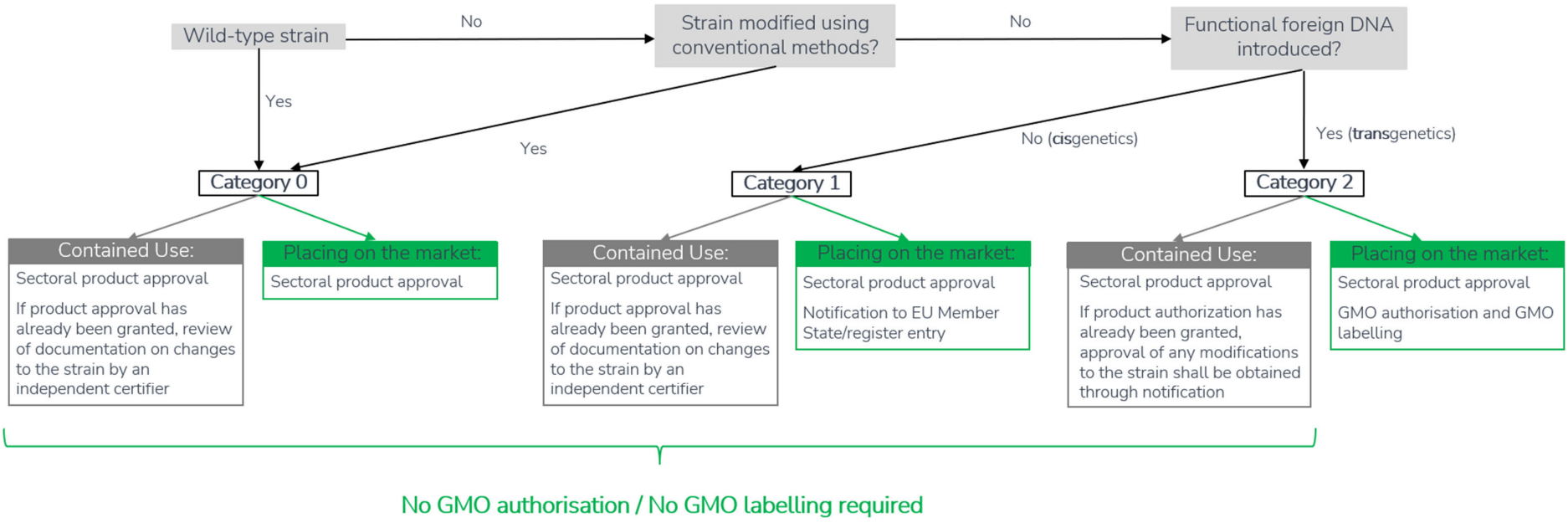

Figure 1: Proposal on the gradual categorisation of microorganisms (decision tree).

6. Case studies and review of the proposed categorisation

Case studies are used to illustrate the challenges of the current regulation. The new regulatory approach proposed here is examined for suitability based on the examples.

6.1. Biomass-containing amino acid products for animal nutrition

Background and issues

Reducing feed costs by balancing the amino acid composition in animal nutrition is a good way to increase efficiency, but it requires precision. Lysine, for example, is an essential and limiting amino acid in feed for poultry, pigs, fish, crustaceans and dairy cows. Lysine deficiency can have a negative effect on the growth performance of animals.

Biolys®, L-lysine sulphate, produced by fermentation with *Corynebacterium glutamicum* DSM 24990, is authorised as a feed additive for all animal species in the EU in accordance with Regulation (EC) No. 2019/1964. In the interests of sustainable production, the inactivated production strain can also be used as a feed additive in addition to lysine. Biolys® therefore contains L-lysine granulated with nutrient-rich biomass. After fermentation is complete, the broth is heated to inactivate the production strain and then water is removed by evaporation and spray drying to obtain the final product. The mixture of lysine and biomass forms the basis of the product – without any waste and without viable microorganisms.

The continuous development of the production strain is an essential aspect of improving the CO_2-footprint for lysine. For the EU product, production must be carried out using *C. glutamicum* DSM 24990, a non-genetically modified strain; otherwise, approval outside the scope of the GMO framework would not be possible. GMO registration would be too expensive and time-consuming in a highly competitive and rapidly changing market. To remain competitive, production strains need to be adapted once a year, making approval times of more than one year unacceptable, not to mention GMO approval of more than five years.

Non-GMO strain technology is outdated and no longer competitive, which is why Bio-lys® production at Evonik's sites in Castro and Blair has already been converted to genetically modified *C. glutamicum* strains, with the result that the markets in North and South America, as well as in the Middle East and Africa, are now being served, but not in the EU.

The latest Biolys® formulation, produced using a GMO strain, contains at least 62.4 % L-lysine and valuable components resulting from the fermentation process – additional nutrients and energy that further benefit farm animals such as pigs or poultry. The latest Biolys® formulation enables customers to meet their animals' essential amino acid requirements even more efficiently. Customers can optimise their feeding to a climate-friendly, low-protein diet. This is fully in line with global efforts to meet the growing demand for high-quality animal protein for healthy human nutrition in a sustainable manner.

Unfortunately, the EU and customers in the EU cannot benefit from these advantages. To achieve this, the scope of Regulation (EC) No 1829/2003[3] on genetically modified food and feed and the terminology of deliberate release/placing on the market would need to be clarified in relation to the contained use of microbial production strains.

Review of the categorisation system

The latest Biolys® formulation is produced using a GMO strain that contains functional foreign DNA. The microbial strain belongs to category 2 according to the proposed classification system. Now to the question of the product's intended use. The answer is contained use. The strain acts as a production strain for producing the amino acid L-lysine and is inactivated in the fermenter vessel. The end product Biolys® does not contain any microorganisms capable of multiplying or transmitting genetic material as defined in Directive 2009/41/EC[6]. Consequently, only product authorisation under sectoral legislation is required. No further GMO regulation is necessary and therefore no GMO labelling is required.

The regulatory proposal discussed in this position paper would allow economically viable EU market access for biomass-containing products produced using GMMs, provided, of course, that the relevant market authorisation has been obtained.

6.2. Modification of production strains within the scope of existing product authorisations for feed additives

Background and issues

Approvals for feed additives such as amino acids, vitamins and enzymes are now linked in the EU to the deposit number of the production strain in an internationally recognised strain collection. The introduction of an improved microbial production strain for a previously authorised feed additive may require the submission of a new, complete dossier in the EU. A new product authorisation is associated with an average authorisation period of approximately two years.

To be and remain competitive in this highly competitive market segment of feed additives, it is necessary, among other things, to continuously improve the strain technology. Modern biotechnological techniques are used to continuously optimise the strains in terms of efficacy, safety and sustainability. The most urgent desire is therefore to move away from a process-centred approach to a product-centred approach in existing GMO legislation (Directive 2009/41/EC[6]. The final product, in this case the feed additive, should be the decisive factor. If there is no change to the specifications set out in the existing product authorisation and, as in this case study, the viable production strain is not contained in the final product, it should be possible to inform the authorities of the strain change and its consequences by means of a notification. The extent of the information required should depend on the changes made to the strain.

Review of the categorisation system

The production strains for the production of feed additives are continuously being further developed. Common changes include, for example, increasing the number of copies of homologous genes and replacing promoters. This increases the metabolic flux into the relevant biosynthesis and/or ensures cofactor availability. In addition, heterologous genes are also integrated into the microorganism, which, in addition to the above-mentioned goals, also enable the effective use of more complex sugars and the export of the product into the fermentation broth. This not only increases product yield but also establishes the usability of residual and side streams, which is in line with the principle of a sustainable circular economy.

If the production strain contains only homologous changes (cisgenetics), it belongs to category 1. If heterologous genes are introduced (transgenetics), this means category 2. Since in the present case study a product has already been approved as a feed additive under Regulation 1831/2003[2], it would be possible to report the strain modification based on the current regulatory proposal as follows. The documentation of category 1 strain modifications is reviewed by an independent certifier. In the case of category 2, prior notification must be given before the strain with the modification can be used.

The regulatory proposal discussed in this position paper would solve the problems outlined above for this case study by implementing accelerated processes for production strain changes.

6.3. Genetically optimised microbial strains for use as probiotics in animal nutrition

Background and issues

The need for sustainable livestock farming is fuelled by global trends such as population growth and the needs of stakeholders in the food chain. By 2050, up to 10 billion people will be living on this planet, leading to increased demand for affordable and accessible sources of protein. Since 2018, poultry has been the dominant source of animal protein. Contrary to general sustainability efforts, 73% of all antibiotics were used in meat production in 2021. Interestingly, most of them were used beyond medical justification as antibiotic growth promoters (AGPs), which are administered in subtherapeutic doses to improve the growth performance of animals. According to the WHO, there is a link between the increasing use of antibiotics in livestock farming and in human and veterinary medicine and the ever-increasing spread of antibiotic-resistant bacteria, which limits treatment options in hospitals. As a result, AGPs were completely banned in the EU from 2006 onwards. However, they are still used in regions outside Europe.

The ban on AGPs in the EU has led to increased interest in feed additives that have the potential to generate comparable effects/benefits. In addition to probiotics, which are considered to have the greatest potential, these feed additives include organic acids, enzymes, prebiotics and phytogenic substances. According to various market studies, the global market for probiotics for animal feed was worth around 2.7 billion US dollars in 2021. There is a great need for effective, scientifically sound probiotics to improve the health and performance of farm animals.

Natural resistance to antibiotics prevents microorganisms that are perfectly suited for use as probiotics from being approved as feed additives in the EU. The technical possibilities for eliminating such properties, which are undesirable for economic use, are available in the form of targeted mutagenesis methods. Regulatory restrictions alone prevent these possibilities from being used effectively. The most direct solution is therefore to fundamentally revise the existing GMO legislation (Directive 2001/18/EC[5]. This requires a shift from a process-centred to a product-centred approach.

Review of the categorisation system

The targeted removal of, for example, natural resistance to antibiotics requires targeted mutagenesis, whereby the strain is genetically modified without introducing (functional) foreign DNA. Based on the proposed categorisation, this means that it belongs to category 1. Since the microorganism is the product, product authorisation is required in accordance with sectoral legislation, i.e. product authorisation as a feed additive under Regulation 1831/2003[2]. Since the risk assessment of the microorganism is part of the product

authorisation, notification/register entry is not required.

The regulatory proposal discussed in this position paper would solve the problem described above for this case study.

6.4. Production of fermented, alcohol-reduced beverages using optimised yeast cultures

Background and issues

In Europe, the focus of vine cultivation is predominantly on fermenting grape must into wine. The *Saccharomyces* wine yeasts traditionally used in this process convert approximately two-thirds of the sugar (> 240 g/L) into alcohol. Due to climate change, the sugar content in must continue to rise (approximately 1% by volume per 17 g). Attempts are being made to counteract the ethanol content, which is rising at the same rate, as health-conscious consumers want to limit their alcohol consumption.

This can be achieved through viticultural measures, the use of *non-Saccharomyces* yeasts (alone or in combination with classic wine yeasts) or genetic modification of *Saccharomyces* strains. However, only single-digit percentage reductions can be achieved. This reduction is too small to actually obtain a non-alcoholic beverage (<0.5% vol.). The latter can currently only be achieved through physical or thermal treatment after fermentation. On the one hand, this is problematic in terms of energy and therefore cost, i.e. it is not very sustainable, and on the other hand, it inevitably leads to a loss of aroma and a change in the flavour profile. The dealcoholised wines produced in this way and currently available on the market, as well as other traditionally fermented non-alcoholic beverages (e.g. kombucha), are not an acceptable alternative for the majority of consumers.

To circumvent this dilemma and meet consumer demand for realistic wine alternatives, beverage yeasts with an ethanol yield reduced by at least 50% would have to be made available. The strategies implemented to date in wine yeast strains to divert the carbon flow away from ethanol have not been successful, as targeted interventions in individual metabolic pathways lead to increased production of sensory undesirable metabolites. In addition, with each further intervention in the metabolic network to compensate for side effects, the overall growth fitness of the strains decreases.

Promising alternative approaches include changes to globally acting regulators and the establishment of parallel metabolic pathways, but these have not yet achieved commercial relevance, particularly due to the process-oriented GMO regulation. Corresponding approaches are made possible using genome editing tools (e.g. CRISPR/Cas):

1) Through the targeted introduction of amino acid substitutions in a globally active *Saccharomyces* regulator (e.g. SPT-15) using CRISPR/Cas technology, wine yeast strains can be produced that exhibit a reduction in alcohol production of around 35%[15].
2) By combining this with "self-cloning" approaches (common modifications include increasing the number of copies of homologous genes, possibly combined with gene deletions and promoter exchanges), optimised wine yeasts with appealing aroma profiles can be generated.

Review of the categorisation system

For both editing measures, it is impossible to determine on the final strain how they originated, provided they were carried out properly. Amino acid exchanges can also occur naturally or be induced by "classical" methods that are exempt from the GMO Regulation. Genome rearrangements are widespread among microorganisms and often represent a massive adaptation to changing environmental conditions.

Foreign DNA is not introduced or is no longer present in the final strain, which can be easily documented by genome sequencing.

The product of fermentation (wine, beer or similar fermented beverages) in a closed system is free from microorganisms capable of multiplying or transmitting genetic material as defined in Directive 2009/41/EC[6]. The strain acts as the production strain for the corresponding beverages and is either inactivated and filtered out in the fermenter vessel or the beverage is pasteurised in the bottle after filtering and bottling.

The microbial strain belongs to category 1 according to the proposed classification system, as it has been proven not to contain any foreign DNA (see above).

Consequently, only product approval in accordance with sectoral legal requirements is necessary. No further GMO regulations are required and therefore no GMO labelling is necessary.

If the microorganism is part of the product (e.g. in kombucha-type beverages), it also falls into category 1, as no foreign DNA has been introduced. Product authorisation is therefore also granted, which includes a risk assessment of the microorganism – notification or register entry is not required.

6.5. Legal uncertainty regarding food cultures

Background and issues

Food cultures include microorganisms that are used in the production of food and are widely used. Examples include dairy cultures for yoghurt or cheese production and cultures used in meat products. The microorganisms are therefore used as such in food production and remain in the product.

Regardless of the GMO issue, such a culture must, of course, always be safe. This is required by general food legislation and is considered to be fulfilled in this example.

Conventional cultures are of natural origin or are produced using specific methods and are currently generally exempt from GMO legislation. Modern genetic engineering techniques (e.g. *gene editing*) can be used to optimise such cultures in a targeted manner without the origin of the modification in the product (the cells of the culture) being precisely traceable. Targeted modification saves valuable development time, can eliminate unwanted characteristics, increase nutritional value (e.g. through higher vitamin content) and extend the shelf life of food. All these advantages are necessary to remain competitive internationally.

A naturally or conventionally mutated culture does not fall within the scope of GMO legislation and may be placed on the market without special authorisation. In contrast, a culture that has been specifically modified using modern techniques (e.g. *gene editing*) would have to be assessed and authorised under current GMO legislation. This also applies if the origin of the modification can no longer be clearly identified based on the culture alone.

This means that one and the same product that has been modified using different techniques could potentially

fall under different EU regulations, without it being possible to determine with certainty which regulation applies when considering the organism alone.

To ensure legal certainty, the applicable legislation should be adapted, and products should be assessed on the basis of their characteristics rather than the way in which they were produced.

With the categorisation system proposed here, authorisation under GMO legislation prior to placing on the market would only be required in cases where heterologous sequences have been integrated into the genome.

Review of the categorisation system

A food culture modified by targeted mutation would fall into category 1, as no heterologous sequences have been inserted. This means that no authorisation under GMO legislation and no labelling would be required. Sectoral product authorisation remains unaffected. To ensure transparency, category 1 cultures would be reported to an EU Member State and entered in a register.

Such a culture, where the origin of the modification can no longer be determined based on the organism alone, would then be regulated in the same way as an indistinguishable conventional culture (apart from being entered in a register).

This would ensure legal certainty for industry and authorities in practice and solve the problem described by the proposed regulation.

7. Consideration of the proposed categorisation in the context of existing international regulatory systems

The following section evaluates the proposed regulatory concept for microorganisms in comparison with other legislation.

It is particularly important for globally active companies that there are no differences with regard to (non-) GMO declaration of an identical product, i.e. a (non-)GMO product in the EU should also be a (non-)GMO product in the USA. Dependencies on the jurisdiction of the country of sale should be reduced as far as possible by harmonising regulatory systems worldwide. In this regard, it is essential to evaluate the proposed regulatory concept for microorganisms in comparison with other legislations.

The EU and the US were leading countries in the introduction of GMO regulations. The GMO regulations reflect the contrasting regulatory principles of the EU's "precautionary principle" and the US's "substantial equivalence". Common elements of GMO regulation in the EU and the US include authorisation, risk assessment, labelling and traceability. Many other countries have adopted one or both approaches in whole or in part and introduced national GMO regulations, resulting in a fragmented global landscape of GMO regulations.

Some countries and territories have adapted their legislation to also cover NGTs and/or NGT products (e.g. Argentina, Australia, Brazil, Chile, Colombia, Honduras, Israel, Japan, Paraguay, USA). The amendments often include exemptions that may be product-based, process-based or a combination of both. However, only a few of these countries have also addressed microorganisms.

In the case of product-based exemptions, the product characteristics determine whether an NGT product falls under GMO legislation or not. Process-based exemptions exclude NGT products obtained through specific techniques. Product- and process-based exemptions can be combined, e.g. to exempt only NGT products

obtained using certain techniques and where the changes to the end product are limited.

Focusing specifically on microorganisms, Table 5 below summarises how genetic modification techniques are generally classified for regulatory purposes worldwide.

The EU could now be an international pioneer with an innovative, forward-looking regulatory concept for microorganisms. The proposed regulatory concept reflects international basic principles very well, such as the introduction of foreign DNA = GMOs. By deliberately refraining from setting restrictions by quantifying possible changes, as in the EU Commission's NGT plants proposal, account is taken of the fact that the use of conventional methods to modify microorganisms already causes a large number of mutations. By using the origin of the sequence (foreign/own DNA) as the decisive parameter for determining whether or not something is a GMO, the aim is to achieve a simple and easily comprehensible categorisation that can also be checked quickly and easily by the competent control authorities.

Table 5: Regulatory classification of genetic modification techniques in the EU compared to other countries.

Genetic modification techniques	Description	Regulatory classification
Conventional methods (e.g. ionising radiation or mutagenic chemicals) that have been in use since the 1930s	Techniques that enhance the natural outcome of mutagenesis are random	Techniques lead to non-GMOs
Genetic engineering tools that have been in use since the 1980s/1990s	Targeted genetic modification leads to a planned result with the possibility of inserting own or foreign DNA	EU (current): Techniques lead to GMOs In other countries (e.g. Argentina, Brazil, USA), classification is based on the origin of the genetically introduced material: Origin of the introduced DNA is the same organism = non-GMO Origin of the introduced DNA is from another organism = GMO

Genetic modification techniques	Description	Regulatory classification
New genomic techniques (e.g. CRISPR/Cas) developed since 2001	Adjustments of genetic material with precision, efficiency and speed Targeted DNA modification based on removing, adding and rewriting sequences allows small changes to be made that do not differ in their results from conventional methods.	EU: Techniques lead to GMOs In other countries (e.g. Argentina, Brazil, USA), classification is based on the origin of the introduced genetic material: same organism = non-GMO different organism = GMO

8. Glossary

Cisgenesis/cisgenetics	A method of plant breeding in which a recipient plant is genetically modified with one or more genes from the same plant or a plant that is related to and crossable with the recipient plant. In cisgenic plants (cis = this side), no natural crossing barriers are crossed. In the context of microorganisms, however, this is referred to as self-cloning, i.e. a genetic modification of the genome in which genetic material from the same species or from a closely related species is inserted. In this proposal for microorganisms, however, the term cisgenetics is deliberately used to ensure consistency with the proposed legislation for plants and to clearly identify the counterpart to transgenetics.
CRISPR/Cas	The CRISPR/Cas system is a molecular biological method that enables DNA to be cut and modified in a targeted manner (genome editing). It is based on "clustered regularly interspaced short palindromic repeats" and the CRISPR-associated protein (Cas). The CRISPR Cas system is naturally part of the bacterial immune system and serves to defend against viruses.
Deletion	A type of mutation in which individual nucleotides or even DNA sequence segments are removed from the genome.
DNA	Deoxyribonucleic acid is a nucleic acid composed of different deoxyribonucleotides that contains the genetic information of an organism. This information is organised in the form of genes. The basic building blocks of DNA strands are four different nucleotides, each consisting of a phosphate residue, the sugar deoxyribose and one of four nucleic bases (adenine, thymine, guanine and cytosine).

Fermentation	Process in which microorganisms such as bacteria, fungi, yeasts and microalgae are used to preserve and/or transform raw materials into e.g. food, feed, chemicals, pharmaceuticals, fuel, biomass.
Gene	The basic unit of heredity. A section of DNA that carries the genetic information responsible for the development, growth and function of organisms. Genes determine the characteristics of a living being and provide the information that is used to produce RNA (ribonucleic acid) "copies" of the genes for the synthesis of proteins.
Genome	The entire genetic material of a cell or virus.
Genome/Gene Editing	Targeted and precise modification of genetic information
Homologous genes	Genes/DNA sequences of the same or closely related-species (cf. cisgenetics)
Heterologous	Genes/DNA sequences originating from another species (cf. transgenics)
Insertion	A type of mutation in which individual nucleotides or DNA sequence segments are inserted into the genome.
Conjugation	Process in which bacteria exchange genetic material, mainly in the form of plasmids, through direct cell contact.
Mutagenesis	Creation of changes (mutations) in genetic material
Targeted mutagenesis	Targeted modification of genetic material using recombinant DNA techniques/genome editing methods.
Mutagenesis, conventional	In conventional mutagenesis, genetic material is randomly altered by exposing a living organism to conditions that cause genetic changes (e.g. UV light, chemicals). Since it is impossible to predict exactly where in the genome a mutation will occur, the desired organism is selected using a suitable screening procedure.

New genomic techniques (NGT)	Modern methods developed after the introduction of EU Directive 2001/18/EC for the targeted modification of the genetic material of organisms, CRISPR Cas being the best-known technique. These methods enable the genetic material of an organism to be modified with precision.
Gene pool	The totality of all genes and their different variants within a population.
Promoter	Section of genetic material that influences how actively a gene is read.
Recombination	Recombination of genetic material
RNA	RiboNucleic Acid, copies of genetic material of varying lengths that perform various tasks within the cell.
Self-cloning	A genetic engineering process in which genetic material (genes or gene segments) is removed from a cell or organism and reintroduced into cells of the same species or a closely related species.
Transduction	Transfer of genetic material between bacteria by viruses or viral vectors.
Transgenesis/transgenetics	Genetic modification of genetic material in which foreign genetic material is inserted.
Transformation	Process in which "free DNA" from the environment is taken up by competent bacteria.
Protoplast fusion	Protoplast fusion refers to the fusion of two cells whose cell walls have been dissolved by enzymes (protoplasts).
Polyploidy induction	The presence of more than two sets of chromosomes in a cell. Chromosomes are packaging units of genetic material. Polyploidy occurs frequently, especially in plants. Polyploidy can be induced by various methods, such as mitosis inhibition.
Wild type / WT	The original, natural form of an organism or gene, as it has naturally evolved.
Breeding, conventional	Process in which, nowadays usually by means of radiation or chemicals, numerous random changes are introduced into the genetic material of a plant and the plants are then selected for new desired characteristics.

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