BIO DEUTSCHLAND
Biotechnologie-Industrie-Organisation Deutschland e. V.

Position paper of BIO Deutschland

Assessment of the legal classification of new genetic engineering methods

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1. Summary

As the sector association of the biotechnology industry, BIO Deutschland recommends using existing regulatory requirements to classify organisms that have been modified by genome editing.

Innovations are an investment in Germany's future viability as a business location. Only through consistent innovation can the German economy remain strong and stand up to international competition. It is therefore important to encourage new research approaches. In biotechnology, new tailored techniques for the targeted editing of genomes have ushered in a new era of research (e.g. CRISPR/CAS9 and similar systems). In addition to physical and chemical mutagenesis, which are treated as recognised methods and exceptions in genetic engineering law and are exempt from regulation, "bio-mutagenesis" should also be allowed without additional conditions.

It is BIO Deutschland's view that new genetic engineering methods can be legally classified on the basis of valid EU GMO legislation (i.e. Directive 2001/18/EC) and its transposition into national law of EU member states:

1. The new genetic variant in the final product should not be included in the scope of EU GMO legislation:
   - if the new genetic variant is the result of spontaneous or induced mutagenesis (through non-targeted methods such as chemical treatment and radiation or targeted methods such as genome editing), or
   - if there are no new combinations of genetic material (e.g. no stable insertion of one or more genes in the genome of the target organism), or
   - if the final product exclusively contains stably inserted inherited genetic material from sexually compatible/crossable species.
2. Products should be included under EU GMO legislation if they clearly and verifiably contain stably inserted genetic material from sexually incompatible species.

For this, it is essential that decisions be made on a case-by-case basis and that methods not be generally subject to regulation by existing GMO law. On the basis of individual decisions, the distinction can be made between naturally genetically modified organisms (NGMOs) and genetically modified organisms (GMOs).

A science-based legal framework for decision making that does not restrict certain methods, is the only way to create an environment in which innovative products can be used in a safe and sustainable way for the benefit of European citizens.

2. Introduction

Innovations are an investment in Germany's future viability as a business location. Only through consistent innovation can the German economy remain strong and stand up to international competition. It is therefore important to encourage new research approaches. In biotechnology, new tailored techniques for the targeted editing of genomes have ushered in a new era of research. These new techniques are being applied in areas such as medicine, agriculture and industrial production.

The last decade has seen rapid advancements in methods for making selective changes to DNA sequences. What today is commonly lumped together under the heading of genome editing, describes a number of methods that enable researchers to selectively turn off, modify and insert genes. These methods are founded on the natural characteristics of enzymes, which can be used to rewrite DNA sequences. At the moment, a system known as Clustered Regularly Interspaced Short Palindrome Repeats/Cas 9, or CRISPR/Cas9 for short, is getting the most attention. Given the intensive research and development that is underway in this area, further genome editing methods are expected to be discovered in the near future.

Slightly modified organisms that arise through genome editing methods are difficult to differentiate from variations that normally occur in the chromosomes, and such differentiation is only possible if the modification process is known in detail. They are very much like mutations that occur by natural means. This key difference from previous methods of genetic modification, which can be demonstrated *a posteriori* through genetic testing, is now the source of a growing number of debates within the discipline and among the general public.

In addition to physical and chemical mutagenesis, which are treated as recognised methods and exceptions in genetic engineering law and are exempt from regulation, "bio-mutagenesis" should also be allowed without additional conditions.

3. Regulation of new methods

Following a science-based approach that aims to protect the public, we believe that both the EU's legal framework and national law ensure adequate safety in terms of the assessment.

In Germany, organisms modified by genetic engineering are subject to the Genetic Engineering Act, which represents a concretisation of EU Directive 2001/18/EC. This legal framework defines a genetically modified organism (GMO) as any organism other than a human being whose genetic material has been modified in a way that is not possible through natural means by crossing and/or natural recombination. The regulation excludes organisms whose genetic modification has arisen through mutagenesis or cell fusion (i.e. organisms that can exchange genetic material by means of conventional breeding).

The existing regulation can be applied to the new genome editing techniques. On the one hand, modification can create organisms that cannot be distinguished from organisms that arise as a result of spontaneous, naturally occurring mutation or that are brought into existence through conventional breeding. For example, the enzyme responsible for copying – and thus doubling – the DNA during cell division makes mistakes. Most of these mistakes are immediately corrected by the cell's internal repair system. However, some of them remain, giving rise to changes in the DNA, known as mutations. The result of these very minor changes – which also occur in nature – is not considered a genetically modified organism (GMO) in the legal sense.

As a rule, individuals of one species are never genetically identical, unless of course they are clones. People differ in their genetic makeup, on average, by 0.1 percent. This means that the genetic makeup of two randomly chosen people differs in around three million places. In addition, children have around 60 new changes in their genetic material that cannot be found in their parents. In other species, such as chimpanzees, fruit flies and corn, there are larger differences within the species than one finds in humans.[1][2]

[1] *The Routledge Companion to the Philosophy of Race*, Paul C Taylor, Linda Martín Alcoff, Luvell Anderson (eds): https://books.google.de/books?id=XJxADwAAQBAJ&pg=PT586&lpg=PT586&dq=nucleotide+diversity+fruit+flies&source=bl&ots=5vMBCQF7RS&sig=-Zv-7eILP1sXpELkcRzSQ0xkJng&hl=de&sa=X&ved=0ahUKEwicyfq7vebZAhUR6KQKHY_WAFY4ChDoAQg8MAM#v=onepage&q=nucleotide%20diversity%20fruit%20flies&f=false.

On the other hand, the use of genome editing can also create products that are subject to GMO legislation,[3] such as when whole genes are introduced. Because of this, it is essential that decisions be made on a case-by-case basis and that methods not be generally subject to regulation by existing GMO law. On the basis of individual decisions, the distinction can be made between naturally genetically modified organisms (NGMOs) and genetically modified organisms (GMOs).

It is BIO Deutschland's view that new methods in genetic engineering can be legally categorised on the basis of valid EU GMO legislation (i.e. Directive 2001/18/EC) and its transposition into national law of EU member states:

1. The new genetic variant in the final product should not be included in the scope of EU GMO legislation:
   - if the new genetic variant is the result of spontaneous or induced mutagenesis (through non-targeted methods such as chemical treatment and radiation or targeted methods such as genome editing), or
   - if there are no new combinations of genetic material (e.g. no stable insertion of one or more genes in the genome of the target organism), or
   - if the final product exclusively contains stably inserted inherited genetic material from sexually compatible/crossable species.
2. Products should be included under EU GMO legislation if they clearly and verifiably contain stably inserted genetic material from sexually incompatible species.

A science-based legal framework for decision making that does not restrict certain methods, is the only way to create an environment in which innovative products can be used in a safe and sustainable way for the benefit of European citizens. Introducing regulatory oversight and slowing innovation will not improve product safety, and it carries the risk of blocking urgently needed innovative solutions for the EU in areas such as medical breakthroughs, better food and feed quality, and environmentally friendly production methods and products.

The European Commission has conducted reviews in the past, particularly in the area of plant breeding, to determine whether products bred using certain genome editing methods should or should not fall under existing regulations.[4] Ultimately, professional opinions from the member states' New Techniques Working Group,[5] from the European Food Safety Authority (EFSA)[6] on a specific genome editing method[7] and from the Joint Research Center (JRC) determined that the EU's existing genetic engineering law as a whole is not suited to the majority of products created using genome editing methods. Considering products individually, on a case-by-case basis, is the necessary and suitable approach.

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[2] **"**New insights into the generation and role of de novo mutations in health and disease", R. Acunda-Hidalgo et al. *Genome Biology*, 2016, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5125044/.

[3] CJEU Advocate General's opinion regarding whether, according to the EU's GMO Directive, CRISPR and other techniques should automatically fall under the definition of GMOs: http://curia.europa.eu/juris/document/document.jsf?docid=198532&mode=req&pageIndex=1&dir=&occ=first&part=1&text=&doclang=DE&cid=538932.

[4] I.e. Directive 2001/18/EC and Directive 2009/41/EC.

[5] New Techniques Working Group: Final Report of the European Commission, 2012.

[6] EFSA Panel on Genetically Modified Organisms: "Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function", 2012, 10:2943.

[7] See: http://onlinelibrary.wiley.com/doi/10.2903/j.efsa.2012.2943/full.

As the sector association of the biotechnology industry, BIO Deutschland has set itself the objective of supporting and promoting the development of an innovative economic sector based on modern biosciences. The association currently has over 300 members. Dr Peter Heinrich is Chairman of the Board of BIO Deutschland.

BIO Deutschland's supporting members and partners are Abbvie, Avia, Bayer Pharma, Boehringer Ingelheim Pharma, Clariant Produkte (Deutschland), CMS Hasche Sigle, Deutsche Bank, EBD Group, EY, Isenbruck │ Bösl │ Hörschler, Janssen, KPMG, Merck, MiltenyiBiotec, MorphoSys, PricewaterhouseCoopers, Qiagen, Roche Diagnostics, Sanofi-Aventis Deutschland, SAP, Thermo Fischer, Vertex and VWR.

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Further information about the activities of BIO Deutschland can be obtained upon request from the association's headquarters or at www.biodeutschland.org.

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