New developments and regulatory issues in plant genetic engineering

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Content

1 Summary and key messages

Genetic engineering is developing at a rapid pace due to technological advances such as genome editing tools like CRISPR/Cas, digitalisation and automation. The European Commission has now proposed a review of the current legal framework for some types of plants derived from new genomic techniques (NGTs) and has published an Inception Impact Assessment.[1]

The European Commission has suggested **two main pillars for a future policy** on genetic engineering: First, the European Commission has highlighted the need to ensure a high level of protection of human and animal health and the environment. Second, the integration of a sustainability analysis has been proposed that is in line with the goals of European Green Deal and its Farm to Fork Strategy, the EU Sustainable Development Strategy and the United Nations Sustainable Development Goals (SDGs). **From the perspective of nature conservation, both pillars are desirable and viable for the future: a high safety level based on the precautionary principle as well as additional proof of sustainability.**

Maintaining a high safety level of protection of human and animal health and the environment

The precautionary principle ensures a high level of protection of human and animal health and the environment. As a provision of primary law (Art. 191 para. 2 TFEU), it is a guiding principle which is binding for all measures taken by the European Union (EU). In cases where scientific uncertainty exists and gives rise to a potential danger to the environment, it must always be initially assumed that there is uncertainty and a potential danger. Both directed mutagenesis and cisgenesis are rapidly developing fields where few if any experience exists with the deliberate release of these plants and the use of their products.

Directed mutagenesis and cisgenesis can be harnessed for a variety of traits with a wide range of intended and unintended impacts. It is important to keep in mind that naturalness and similarity to breeding does not imply safety. In addition, small changes can also have considerable impacts: at the level of metabolism, the exhibited characteristic of the genetically modified organism (GMO) and on the receiving environment. Also, in contrast to breeding, genome editing makes the whole genome accessible for changes. In return, this also means that directed mutagenesis increases the depth of intervention and is thus not comparable to conventional breeding including random mutagenesis.

Risks may arise from both the intended and unintended characteristics. For example, drought resistance could change the plants' invasiveness and, as a consequence, pose a risk to vulnerable plant communities, e.g. in arid and ecologically valuable locations. For the risk evaluation, it is irrelevant whether the introduced characteristics of a plant are novel. Drought resistance is an example of a trait that may not be novel, but can entail environmental risks. Besides the negative impacts of the introduced characteristics, modified plants can exhibit unintended characteristics that originate either from adverse genetic effects or from unintended changes in the plant's metabolism triggered by the intended trait. Some traits like herbicide and insect resistance in plants have also not

[1] European Commission Legislative Proposal, "Legislation for plants produced by certain new genomic techniques" Ref. Ares(2021)5835503 - 24/09/2021. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques_en

proven to be sustainable in the past. **Here we conclude that plants produced by both directed mutagenesis and cisgenesis have a similar if not greater risk potential compared to the plants produced by genetic engineering to date.**

Grouping certain NGTs depending on their risk profile has been discussed. In general, traits cannot be categorised and deemed less risky. From a scientific point of view, no criteria exist which would allow these NGTs to be grouped in a general manner. The size of the genetic modification – for example – cannot be regarded as a reliable denominator of risks and safety of the specific modifications in an individual plant. **Only a case-by-case analysis as performed under the current legislation can ensure a high safety level.**

The genetic engineering law already takes different risk profiles into account on this case-by-case basis. Here we argue that **the EU's current legislative framework is fit for purpose especially in terms of the risk assessment.** Directive 2001/18/EC was amended in 2018 in order to adapt to technical progress, taking into account experience gained in the environmental risk assessment of genetically modified (GM) plants.[2] Also, Directive 2001/18/EC allows for flexibility because the scope of the environmental risk assessment is determined on a case-by-case basis. The required information may thus, under present legislation, already vary depending on the type of the GMOs concerned, their intended use and the potential receiving environment.

In addition, **the genetic engineering law** is the **best regulatory framework** to address the specific hazards arising from the release and placing on the market of GMOs. Other legislative frameworks, e.g. European seed legislation, are not suitable. **The European genetic engineering law needs to remain unfragmented.** The European legislator has established a coherent, independent and complete regulation for GMOs with the complementary Directives 2001/18/EC and 2009/41/EC. This systematic approach is necessary in view of the fact that other legislative acts, such as European seed legislation, food and feed legislation, as well as plant protection and plant variety protection legislation, already serve other purposes. Integrating GMOs into these regulatory systems would therefore not be appropriate either from a scientific or legal perspective.

Despite claims of challenges in identifying NGTs, so far there has been no known case where applicants failed to provide a method to detect or identify a plant derived by NGTs for which they are seeking approval. Directive 2001/18/EC is sufficiently general to allow applicants to develop detection and identification methods, taking into account further technical developments in the field. There is no need to change the respective legislative requirements, which consistently implement the polluter-pays principle (Art. 191 para 2 TFEU). An international GMO registry, however, would greatly improve detection and identification of unapproved GMOs in the EU.

Limited relevance of current NGT-based plants for EU-level strategies and SDGs

The development of NGT plants is often equated with the achievement of sustainable agriculture, assuming that new plant varieties can substantially contribute to policy goals. However, the assumption that the envisaged goals could be achieved in short timeframes, e.g. the 2030 period of the European Green Deal, is not substantiated by scientific analyses. Currently, only a few NGT-based plants are close to entering the market. In addition, the extent to which new plant varieties

[2] COMMISSION DIRECTIVE (EU) 2018/350 of 8 March 2018 amending Directive 2001/18/EC of the European Parliament and of the Council as regards the environmental risk assessment of genetically modified organisms

developed by NGTs could realistically contribute to food security, to biodiversity conservation or the adaptation of agriculture to climate change remains unclear and uncertain at present. The political goals mentioned before are complex and multi-layered. NGT-based plant varieties designed for this purpose need to respond to several environmental stimuli at the same time. Traits such as abiotic stress tolerances are highly complex and therefore usually still at a very early stage of development.

The cornerstones of resilient and sustainable agriculture can therefore currently best be achieved by changing agricultural practices. For example, soil quality and integrated pest management play a major role. Cultivation systems can, for example, increase the soil's water-retention capacity and its ability to store water and nutrients over the long term.

Integration of proof of sustainability in future policies

A binding sustainability analysis is based on established policies. Established international policies at the level of the CBD (as well as most recently in the EU: European Green Deal, Farm to Fork Strategy, EU Sustainable Development Strategy) provide a **convincing basis for including a sustainability analysis** in the assessment of new technologies. A technology assessment can serve as a science-based tool to operationalise a binding sustainability analysis and proof of benefit. The German Federal Agency for Nature Conservation (Bundesamt für Naturschutz, BfN) is currently working on operationalising a technology assessment. This integrated scientific assessment goes beyond current statutory risk assessment by taking into account societal needs as reflected in the SDGs and requiring proof of its benefit for society or the environment. With regard to the assessment of sustainability and the benefit, it should be noted that these are additional instruments aimed at strengthening the goals of the European Green Deal and its Farm to Fork Strategy, the EU Sustainable Development Strategy and the United Nations SDGs. Only the safe use of new technologies will enable the resulting opportunities to be fully harnessed and ensure their long-term use. **It is essential that the precautionary principle be applied to ensure that the measures taken to implement the policies do not lead to results that contradict their underlying aims.** The protection of the environment must therefore always be considered separately when defining and implementing EU policies and measures. At the end of this paper, we propose the most important issues and criteria to consider in order to achieve these goals for the impact assessment – once all policy options have been described and defined in more detail.

2 Introduction

Based on its study of NGTs[3], the European Commission published an Inception Impact Assessment (see footnote 1). It proposes reviewing – and potentially changing – the current legal framework for some kinds of NGT plants and their food and feed products. According to the Commission, this measure is particularly urgent in view of the potential contribution of certain NGT plants to the sustainable agri-food system objectives of the European Green Deal and related sustainability policies.

From a nature conservation perspective, we recognise the urgency of the converging challenges of climate change, biodiversity loss and the sustainable transformation of the agri-food system. We therefore need measures that resolutely address the *causes* of the problems. The highest priority must be to end the overly intensive use of land and water resources. The urgency of these challenges does not imply that the latest technological advances – in this case, NGT plants – offer the most potent solutions – nor does it legitimise undermining the precautionary principle.

The BfN is the central scientific authority of the German government for both national and international nature conservation. This paper contributes to the discussion from a scientific point of view, with a special emphasis on the perspective of nature conservation. We outline how the precautionary principle can be upheld while the most efficient tools for making the agri-food system more sustainable are selected. The paper follows roughly the outline of the Inception Impact Assessment: the context and assumptions are examined, possible policies are assessed and proposed and criteria against which future legislative proposals should be measured are discussed.

3 Context and problems

Some important aspects of the overall situation will need to be taken into account for the upcoming impact assessment. Directive 2001/18/EC was amended in 2018 in order to adapt to technical progress. Directive 2001/18/EC allows for flexibility in the environmental risk assessment, stating that it should be carried out on a case-by-case basis. This implies that the required information may vary depending on the type of GMOs concerned, their intended use and the potential receiving environment. It will be important to evaluate whether new legislation measures are legitimate for plants and products derived from directed mutagenesis and cisgenesis. The 2018 amendment to Directive 2001/18/EC was based on experience gained during the environmental risk assessment of GM plants. In contrast, the current initiative for directed mutagenesis and cisgenesis is based on a limited body of literature and on highly contested considerations. So far, little – if any – experience exists with the deliberate release of plants obtained from directed mutagenesis and cisgenesis and with the use of their products. As a result, the Inception Impact Assessment should focus on the current legislative framework. Especially since it is – as we have analysed here – fit for purpose for

[3] European Commission Staff Working Document "Study on the status of the new genomic techniques under Union law and in light of the Court of Justice Ruling in Case C528/ 16", SWD(2021). https://ec.europa.eu/food/plants/genetically-modified-organisms/new-techniques-biotechnology/ec-study-new-genomic-techniques_en

NGTs, especially in terms of the risk assessment. It will be important to also evaluate measures outside a legislative initiative that can serve the environmental sustainability goals.

It will also be important to take into account all perspectives in the evaluation of the Directive (see footnote 1). The Inception Impact Assessment spans a wide range of issues, starting with the evaluation of the Directive in 2010-2011 to the Commission's current study. However, the evaluation report published in 2010 is primarily relevant for the issue at hand. The concerns – that the legislative framework is not suitable to ensure that the EU can make use of new developments – were not universally shared and in particular less so by the competent authorities.

The impact assessment is also **not fully clear in terms of the scope it seeks to address**. It proposes a legal framework for plants developed by directed mutagenesis or cisgenesis, with alterations of the genetic material that can also be obtained by natural mutations or conventional breeding techniques, noting without further consideration that also more complex alterations can be obtained. However, two central questions remain unanswered. (1) What is meant by alterations of the genetic material? Is it the trait (phenotype) that is subject to the comparison (can also be obtained by) or is the genotype meant instead? From our point of view, the phenotype and the genotype should be compared, and the latter should not be restricted to the intended sequence. (2) Is the idea that "alterations that can also be obtained by natural mutations or conventional breeding techniques" a general and bold statement or does it refer to a characteristic of the plants and products for which the initiative proposes new legislation? Considering the objectives and general principles of the environmental risk assessment of the EU's current GMO legislative framework, we assume that the latter applies. However, this will need to be clarified.

Finally, an assessment is needed to ensure that current legislation also allows for contributions to societal challenges, especially sustainability, to be taken into account when evaluating GMOs. The Inception Impact Assessment states that the current legislative framework does not consider whether products have the potential to contribute to societal challenges, sustainability in particular. This disregards the fact that Articles 7(1) and 19(1) of Regulation (EC) No 1829/2003 allow "other legitimate factors" to be considered, as stated and recognised in the 2010 evaluation of the GMO legislation.

3.1 Limited relevance of current NGT-based plants for EU-level strategies and SDGs

Many stakeholders expect crop varieties produced by NGTs to contribute to achieving the sustainability and productivity goals formulated in the Green Deal, the Farm to Fork Strategy, the EU Biodiversity Strategy for 2030 and the United Nations SDGs. NGT plants with a wide variety of traits are expected to contribute to more sustainable agriculture and food production. This does not only include plants resistant to diseases, pests and the effects of climate change, but also plants that require fewer agricultural inputs (such as water and fertiliser) or plants that could be beneficial to health due to altered nutrient content.

However, the assumption that the envisaged goals could be achieved in short timeframes (e.g. by 2030 for the European Green Deal or SDGs) is not reflected by the current state of research and development. In addition, the extent to which new plant varieties could realistically contribute to food security, to biodiversity conservation or to the adaptation of agriculture to climate change is uncertain at present. The political goals mentioned before are complex and multi-layered. Plant

varieties designed for this purpose need to respond to several environmental stimuli at the same time. However, the complex genetic interplay that occurs when many traits are involved is not yet fully understood. Envisioned characteristics are therefore often difficult to achieve to an extent that could actually contribute to achieving political goals within a reasonable timeframe. It is possible that currently the most promising solutions instead focus on changing agricultural practices, e.g. with increased diversity of cultivated plants leading to more resilient agro-ecosystems and by promoting research on innovative plant breeding strategies like population breeding.

The state of development of plant varieties supporting sustainability objectives

Despite the rapid pace of research and development of NGT-based plants, only a few products from plants obtained with NGTs are available on the market. Currently, it is difficult to fully clarify which additional plants derived from NGTs can be expected in the near future because the relevant data is often not published or partly contradictory (Parisi and Rodríguez-Cerezo, 2021; Ricroch et al., 2021). However, there is some consensus that fewer than 30 applications are currently beyond the development stage. Many of these plants are developed for resistance to biotic stressors, such as pests or diseases, as well as to herbicides. Another significant group of plants produced with NGTs has a modified composition, e.g. their nutrient content or industrially relevant components have been altered. Reports on agronomic traits such as increased yield differ among studies. Plants in advanced stages of development with abiotic stress tolerances, i.e. to drought, heat, salt or waterlogging, are very rare. To date, there is also little scientific evidence on the extent to which crops produced with NGTs will realistically have and express the intended traits, and whether the trait would actually contribute to the stated goals of sustainable agriculture. **This is partly due to the fact that traits intended to benefit sustainability, such as drought tolerance, are complex, context dependent and at present not well defined.**

Plants that respond flexibly to climate stressors are generally still at early stages of development. Contributions of plant breeding to climate adaptation focus on tolerance to abiotic stress, but these traits are typically complex. The physiological adjustments mostly involve superordinate pivot points in metabolism, and subsequent effects are often not fully understood. This also poses new challenges for risk assessment as the complexity of risk profiles also increases (see section 3.2). **In addition, physiological changes are still more static and do not enable adaptation to changing weather extremes that become more prevalent as climate change progresses.** For example, plants with an altered drought response may tolerate drought conditions at a certain developmental stage, such as flowering, but not at seed filling. Each line must therefore be tested in field trials, but even for the most prominently discussed example – drought tolerance – there are only a few publications on field trials. While there is intensive research on more flexible and resilient crops, it will take a long time to reach the market.

Several of the plants expected to be available for commercial use by 2030 carry genes for herbicide resistance. Herbicide resistant plants produced with classical genetic engineering techniques have been available since the 1990s. Their cultivation was originally intended to lead to a decline in the use of pesticides. However, a rising number of weeds has lost its susceptibility to pesticides, giving rise to negative effects for agricultural biodiversity. GM crops with multiple resistances – known as ”stacks” – are now increasingly being cultivated to circumvent these shortcomings. As a result, herbicide use has increased in the medium and long term (Schulz et al., 2021; Schütte et al., 2017).

In the recent past, research has increasingly developed new strategies to create pathogen and fungal resistances that involve altering a plant's susceptibility without using transgenic toxins. In terms of pest management, it remains to be seen whether applications are efficient in the long run, and whether trade-offs for plant metabolism can be avoided.

On closer inspection, many of the plants expected to be available on the market facilitate maintaining specific agricultural practices or industrial production rather than addressing sustainability objectives. The contribution of NGT-based crops to promoting human health is equally questionable. Products with altered nutritional properties, reduced harmful components or prolonged shelf-life address only very specific issues and are primarily suited to promote consumer acceptance of NGTs.

Despite acceleration of genetic modification by NGTs, crop development remains time-consuming

NGTs contribute to speeding up the development of new plant varieties. However, as with conventionally bred varieties, there are various steps to consider before NGT-based plants could contribute to political objectives. The main advantage for directed mutagenesis lies primarily in basic research to determine the genetic background of plant traits and to test a large number of different lines in parallel. How quickly and exhaustively the genetic background of traits can be determined and introduced into plants thus usually depends less on the biotechnological tools than on the complexity and knowledge of traits.

If the existence of a trait is ultimately established in a plant under laboratory or greenhouse conditions, it is still not guaranteed that this trait will be expressed the same way in the field (Massel et al., 2021). Here, changing environmental conditions may lead to unexpected responses of plant metabolism. This may involve yield losses, for example, if the integrity of plant metabolism is compromised. Most data from field trials has not yet been collected so **it remains unclear whether the expected function is fulfilled and the benefit actually materialises**. Moreover, as long as clear definitions of complex traits are lacking, **whether or not a trait is deemed to have been achieved is left solely to the seed producer**.

Once a seed producer considers a plant ready for market, even without GMO regulation, seed approval would be necessary in most European countries. This usually involves a minimum of two years of seed cultivation and testing.[4] After a seed is launched on the market, the plants need to be accepted by market participants, and cultivation systems may have to be converted on a large scale. Hence, even when plants are already available on the market, it cannot be expected that the assumed positive effects will occur quick and easily.

Ultimately, combinations of traits such as drought and heat tolerance with pathogen resistance would be necessary. Some of these traits are already very complex on their own, and it is currently almost impossible to combine them. So far, only a few and mostly simple properties have been combined. If, for example, plants with modified fatty acid profiles were cultivated in the field, they would still have to be irrigated and fertilised by conventional means and would thus eventually contribute to promoting human health, but not to sustainable agriculture at the same time. On the

[4] e.g. for Germany, see https://www.bundessortenamt.de/bsa/sorten/sortenzulassung/

contrary, the possibility cannot be ruled out that these changes put a greater strain on plant metabolism and thus increase the need for additional agricultural inputs.

Changes in agricultural practices are cornerstones of resilient and sustainable agriculture

To achieve climate-resilient plant varieties, another possible approach could be to modify complex traits through selection pressure and population breeding that aims at **increasing the genetic diversity of crop populations**. Supported by smart breeding and high-throughput methods, these approaches are used in particular to develop plants that need to respond flexibly to changing environmental conditions (e.g. weather extremes) that require many coordinated metabolic responses. To reduce the use of herbicides, more research could be carried out to develop **fast-growing varieties that suppress weeds** until the field is covered with the crop plant. These crops can contribute to conventional farming by reducing the need for herbicides, and to organic farming by reducing the management workload.

However, variety selection is only one of many necessary measures. For sustainable and more climate-resilient cultivation that simultaneously protects European biodiversity, nature and the services they provide, **soil quality and integrated pest management also play a major role** (Nabel et al., 2021). Cultivation systems can, for example, increase the soil's water-retention capacity through extended crop rotations and adaptation of soil properties (such as humus structure) to ensure long-term storage of water and nutrients. This also plays a major role in root system growth and the composition of soil ecosystems in the rhizosphere. It can be assumed that as of today, adapting farming conditions can contribute more to sustainability objectives than the few NGT-based varieties currently on the market or those that will be developed in the future. Soils with intact ecosystems can also **contribute to capturing carbon dioxide** as well as environmental contaminants, and they **reduce the need for artificial fertilisers**. This means that, regardless of which crop variety is finally grown, adjustments to agricultural systems and practices will ultimately be necessary anyway for more climate-resilient and sustainable agriculture. This approach should also be reflected in CAP Strategic Plans of EU Member States (Selig et al., 2021).

3.2 Safety and risks of directed mutagenesis and cisgenesis

A key objective of genetic engineering regulation is to prevent harm to human health and the environment. Applications of directed mutagenesis and cisgenesis are powerful instruments to change the characteristics of plants. As a result, plant varieties altered by these NGTs may also exhibit changes that can entail risks for human health and the environment. These risks can stem from the modified plants' intended as well as unintended characteristics.

For example, drought resistance could change the plants' invasiveness and, as a consequence, pose a risk to vulnerable plant communities in arid and ecologically valuable locations. In this context, it would be irrelevant for the risk evaluation whether the introduced characteristics of a plant are novel or not. Besides the potential negative impacts of the intended characteristics, modified plants can exhibit unintended characteristics that stem either from adverse genetic effects or from unintended changes in the plant's metabolism triggered by the intended trait.

On a general note, it should be kept in mind that NGTs are not static, but subject to intensive research and development. The technologies develop rapidly and have not yet reached their full range. New specificities will need to be evaluated for new and as yet unknown effects. Here, we

conclude that plants produced by directed mutagenesis or cisgenesis have a similar – if not greater – risk potential compared with plants produced by conventional genetic engineering.

Naturalness does not imply safety

Since NGTs and their field of applications are constantly evolving, it is becoming increasingly difficult to distinguish between them. This is particularly true for directed mutagenesis compared to other techniques (e.g. transgenesis), methods and even natural processes. Certain traits or characteristics that are now being reproduced by means of directed mutagenesis and cisgenesis already occur in nature. While humans cannot prevent evolutionary events, they do have to take responsibility if they actively modify organisms through genetic engineering. It is often assumed that a potentially high degree of similarity with naturalness implies a lower risk *per se*. However, this kind of comparison does not yield valid indicators and is not suitable for risk assessment. **The risk profile does not depend on whether a genetic change is already present in nature or can theoretically also be obtained through breeding.** The risk potential of directed mutagenesis and cisgenesis – as well as their potential accompanying unintended effects – must therefore be assessed on a case-by-case basis. The precautionary principle has to be upheld and responsibility accepted for changes brought about by humans.

A common toolbox for directed mutagenesis and transgenesis

In its judgment in case C-528/16, the European Court of Justice (ECJ) found that organisms modified using directed mutagenesis are GMO and fall under the scope of Directive 2001/18/EC. Directed mutagenesis is therefore clearly a technique of genetic engineering. The ruling is partly based on the fact that the risks associated with applications of directed mutagenesis are comparable to the risks of transgenesis.

Applications of NGTs share many (directed mutagenesis) or all (cisgenesis) techniques with transgenesis, which in turn means that comparable risks cannot be ruled out without a **case-by-case** analysis of each GMO. In this respect, the EU biotechnology framework has the clear advantage that the risk assessment is process-based (Eckerstorfer et al., 2019a). There is also consensus that genome editing tools generally have the disadvantage of potential adverse effects, **off-target effects** in particular, which may be associated with the targeted sequence (Eckerstorfer et al., 2019b). This is in contrast to random mutagenesis where there are neither target nor off-target sequences. In addition, directed mutagenesis can cause various molecular changes at and near the target sequences (known as “on-target effects” (Eckerstorfer et al., 2021); their occurrence and incidence have not yet been systematically investigated, but need to be assessed on a case-by-case basis.

Directed mutagenesis: small changes can have significant effects

Directed mutagenesis and cisgenesis can be used for many different purposes, but the number and type of changes do not necessarily correlate with risk as this can depend on the technology used, the desired trait and other specific properties of the modified plant. The ECJ clearly distinguishes between directed mutagenesis and random mutagenesis because the former can change organisms much faster and more extensively than the latter, which has long been considered safe. While directed mutagenesis and transgenesis have many common features, certain types of changes are only possible using directed mutagenesis. Examples include directed changes in native genes that enable the modification of entire metabolic pathways (Kawall, 2021), *de novo* domestication of wild relatives of cultivated plants (e.g. Zsögön et al., 2017), or the manipulation of two (or more) genes

(EFSA Panel on Genetically Modified Organisms, 2021) that are genetically linked. In fact, this is one of the main reasons why genome editing tools have been adopted so quickly, e.g. in the field of plant biotechnology: "genome editing makes the whole genome accessible for changes" (Kawall, 2019). In return, this also means that directed mutagenesis increases the **depth of intervention** and is thus not comparable to conventional breeding techniques (Eckerstorfer et al., 2021). In the future, multiple, parallel and stacked changes in the same plant, referred to as **multiplexing by directed mutagenesis and/or cisgenesis,** will be the standard application of NGTs. This is, for example, highlighted by the case study applying **directed mutagenesis** for the knockout of several genes responsible for gluten in wheat, which was selected by EFSA for their recent opinion on Synthetic Biology (EFSA Panel on Genetically Modified Organisms, 2021). It is still extremely difficult to extrapolate the future potential and risks of genome editing, which – if the technology is to be used safely – need to be strictly regulated and assessed on a case-by-case basis.

Directed mutagenesis can be harnessed for many different traits with a wide range of impacts

The recent study on new genome techniques by the European Commission concludes, among other things, that a variety of genome-edited plants will be placed on the market in the short or medium term (see footnote 3). I**n general, traits cannot be categorised and deemed less risky, but require a case-by-case analysis to determine whether the precautionary principle has been upheld**. Some traits cannot be achieved through conventional breeding or within the relevant timeframes. However, potential **risks emerging from *all* traits need adequate assessment**. Directed mutagenesis can produce organisms that are highly relevant to risk areas tested in the environmental risk assessment of GM higher plants according to European legislation. For these or comparable applications of directed mutagenesis, six out of seven risk categories may be directly affected.[5] For example, plants resistant to abiotic stress may show increased *persistence and invasiveness* in the environment and are at the same time able to transfer these traits to wild relatives by *plant to plant gene transfer*. Resistance to certain diseases can be associated with increased susceptibility to another disease (trade-off), which requires evaluation. Enhancement of intrinsic plant defence (e.g. by producing toxic substances) against *target organisms* (e.g. insects) requires assessment and may be associated with adverse effects on *non-target organisms*. Risks can also emerge from the adoption of *old* traits, which have been produced using e.g. transgenesis and some of which have already been introduced in new varieties through directed mutagenesis. The most prominent example, herbicide resistance, enables and results in *impacts on the specific cultivation techniques* that can cause indirect long-term detrimental effects for humans and the environment. It does not therefore comply with the goals of the EU Green Deal and its Farm to Fork Strategy.

3.3 Evaluation of the current legislation

The EU's current legislative framework for GMO is still **fit for purpose,** especially in terms of the risk assessment, but also with regard to detection and identification. Directive 2001/18/EC was amended

[5] Directive 2001/18/EC lists seven relevant areas of risk to be considered in the environmental risk assessment of GM higher plants (GMHP) in Annex D.2: 1. Persistence and invasiveness of the GMHP, including plant to plant gene transfer; (2. Plant to micro-organisms gene transfer -> only applicable if transgenic DNA remains in final product); 3. Interactions of the GMHP with target organisms; 4. Interactions of the GMHP with non-target organisms; 5. Impacts of the specific cultivation, management and harvesting techniques; 6. Effects on biogeochemical processes; 7. Effects on human and animal health.

in 2018 in order to adapt to technical progress and include experience gained in the environmental risk assessment of GM plants (see footnote 2). In addition, Directive 2001/18/EC allows for sufficient flexibility, for example in the environmental risk assessment stating that it should be carried out on a case-by-case basis, meaning that the required information may vary depending on the type of GMO, its intended use and the potential receiving environment.

Detection and identification requirements have not been shown to prevent authorisation of GMOs

According to GMO legislation, applicants are required to provide methods for the detection and identification of GMOs. Despite claims of challenges in identifying NGTs, so far there has been no known case where applicants failed to provide a method to detect or identify a plant derived by NGTs for which they are seeking approval. European genetic engineering law has always placed the "burden of proof" for providing evidence of GMOs in the context of applications for authorisation on the applicant (see, for example, reference no. 36 of Regulation (EC) 1829/2003, Article 5 para. 3 (i) of Regulation (EC) 1829/2003). The application documents for GMO food and feed applications must therefore meet the other requirements laid down in Regulation (EU) 503/2013. This consistently implements the polluter-pays principle under environmental law, which has primary-law status via Article 191 para. 2 TFEU. It states that environmental damage should as a priority be rectified at source and that the polluter must bear the burdens of direct and indirect government monitoring measures. It is therefore only consequential that a verification procedure meeting the legal requirements be required for authorisation. Any financial, material or personnel costs that occur in compliance with an applicable law are not a viable argument for the need to amend legal standards that are necessary to comply with European primary law principles (Spranger, 2021a). Directive 2001/18/EC is sufficiently general to allow applicants to develop detection and identification methods taking into account the other technical developments in the field. Quantification methods used today were less complex back in 2001 when the Directive was adopted. It has to be kept in mind that future detection and identification methods will make use of state-of-the-art methods for DNA sequencing and take into account the environment of the altered target sequence of the DNA to enable identification of the event generated by directed mutagenesis. The potential problem of identification will be less pronounced with the expected adoption of stacking and multiplexing of DNA sequence changes, which help increase certainty.

Environmental and technical law is based on undefined legal terms

The Commission's claim in its study as well as in the Inception Impact Assessment that some undefined legal terms (e.g. "mutagenesis", "conventional use in a number of applications", "long safety record") are legally unclear and pose a problem, is not convincing on its own. Environmental and technical law only exists and functions when undefined legal terms are used. This already results from the fact that a legal analysis and evaluation always has to be carried out in the individual case. The relevant provisions, however, may not represent individual case laws, but instead need to provide more generalised specifications. Still, when using the legal methodology, it is then legally possible to clearly define the meaning for every individual case. The ECJ has clearly shown in its judgment of 25 July2018, C-528/16 that the use of the legal methodology defines the requirements of the "long safety record" (Recital 17 of Directive 2001/18/EC) as well as the concept of "mutagenesis". In addition, every amendment or modification of existing law inevitably leads to new "indeterminate legal concepts", which in turn would require a more concrete definition. As a result, changing the EU Directive may lead to additional uncertainties in this regard, when at the same time

the current Directive 2001/18/EC has shown to be functional and operational using these terms for two decades.

International trade laws enable nature conservation

The blanket assertion that any difficulties arising from the challenge to the existing regulation on the verifiability of NGTs could lead to barriers to trade is not credible. In particular, the existing possibilities in world trade law (WTO law) should be referenced to justify different regulations. This is because WTO law like the "Agreement on Sanitary and Phytosanitary Measures" (SPS) also allows measures to restrict trade in principle if they are considered necessary according to a scientifically based risk assessment and if they were based on non-arbitrary and justifiable considerations (Art. 2 para. 2 and Art. 5 para. 5 and 6 SPS). These conditions are met in the distinction made by the ECJ between conventional mutagenesis and new techniques. The "Agreement on Technical Barriers to Trade (TBT)" also explicitly allows necessary restrictions on trade in the interest of environmental and health protection as well as consumer protection (Art. 2 para. 3 sentence 3 TBT) and, due to its scope of application to technical standards, would in any case only concern labelling or traceability rules, but not the fundamental assessment of new techniques (Spranger, 2019).

4 Main pillars for future policy

The European Commission has suggested **two main pillars for future policy** on genetic engineering:

First, to ensure a **high level of protection of human and animal health and the environment**.

Second, the **integration of a sustainability analysis** that is in line with the goals of the European Green Deal and its Farm to Fork Strategy, the EU Sustainable Development Strategy and the United Nations SDGs.

From the perspective of nature conservation, both pillars are desirable and viable for the future: a high safety level based on the precautionary principle as well as the integration of a sustainability analysis, which should include proof of benefits for society.

4.1 Prerequisites for the protection of human and animal health and the environment

A high level of protection of human and animal health and the environment can only be achieved on the basis of the precautionary principle, which is enshrined in primary law.

The precautionary principle as a provision of primary law

The precautionary principle (Art. 191 para. 2 sentence 2 TFEU) is a guiding principle, which is binding for all measures taken by the European Union (EU). The precautionary principle requires the EU to adopt preventive environmental policies designed to prevent environmental damage in the first place instead of dealing with its effects after the fact. Only when this principle is consistently implemented can an appropriate regulatory basis be ensured. The precautionary principle was specified in further detail by the ECJ (ECJ judgment of 25 July2018, C-528/16) in genetic engineering law in such a way that in cases where scientific uncertainty exists and gives rise to a potential danger to the environment, it must always be initially assumed that there is uncertainty and a potential danger. As we have shown in section 3, in the case of NGTs, both can be assumed from a scientific point of view. To comply with the European primary law provisions, the precautionary principle must therefore be the undisputable standard for the level of protection of human and animal health in future policy.

The purpose of the European GMO legislation is to ensure that risks for the protection of human health and the environment are monitored (Recital 3 of Directive 2001/18/EC or Recital 3 of Regulation (EU) 2017/625) and that the precautionary principle is upheld in all implementation steps (Recital 8 of Directive 2011/18/EC). The recognition of the polluter-pays principle, which is laid down in primary law as well, must equally be fully upheld (Art. 191 para. 2 TFEU). The ECJ has moreover explicitly emphasised (ECJ judgment of 15 April 2021 - C -733/19) that Art. 11 TFEU, which stipulates that environmental protection requirements must be integrated into the definition and implementation of Union policies and activities, does not contain any obligation to promote innovation and technological development. This means that the protection of the environment must always be considered separately when defining and implementing EU policies and measures. The protection of the environment is independent from any specific purpose or goal of innovation. Although scientific and technical progress should, according to the TFEU, be promoted regardless of their concrete purpose (Art. 3 para. 3 TFEU), it must be emphasised that this is a political objective, not a legal principle.

Genetic engineering law is the best framework for ensuring a high level of protection

Genetic engineering law aims to address the specific hazards arising from the release and placing on the market of GMOs. The European legislator has therefore established a coherent, independent and complete regulation of GMOs with the complementary Directives 2001/18/EC and 2009/41/EC. This systematic approach is already explained by the fact that other legislative acts, such as European seed legislation, food and feed legislation, as well as plant protection and plant variety protection legislation, serve other purposes and therefore integrating GMOs into these regulatory systems would not be appropriate from a legal or scientific standpoint. European seed law, for example, aims to ensure sufficient and efficient plant varieties for agriculture. Seed law is also not designed to assess specific dangers that could arise from the use of high-tech processes like genome editing. This applies equally to the law on the authorisation of plant protection products, which is limited to active substances of plant protection products (Spranger, 2017).

The aim of any political initiative must therefore be to prevent fragmentation of the law. Moreover, in terms of administrative organisation, fragmentation of this kind would also lead to a situation where different authorities would have to act within their respective limited scope of responsibility. The result would be that the currently existing in-depth expertise of the authorities, which arises from the fact that they are solely responsible for the implementation of genetic engineering law, could no longer be equally granted for the application of biotechnology.

Genetic engineering law takes different risk profiles into account on a case-by-case basis

The instruments and outcomes of the genetic modifications of directed mutagenesis and cisgenesis are diverse. In addition, techniques have not reached their full range. At this point in time, a full assessment of future potential risks from any given technique is not within the realm of possibility. Viable future legislation that is able to keep pace with scientific developments has to take into account the dynamic growth of technological developments. In view of the dynamic nature of technological developments and the uncertain risks involved, the ECJ has emphasised the importance of the precautionary principle in its judgement of 25 July 2018, C-528/16.

Grouping certain NGTs depending on their risk profile has been discussed. However, from a scientific point of view, no criteria exist which would allow these NGTs to be grouped in a general manner. For example, it has been shown (section 3 and Eckerstorfer et al., 2021) that the size of the genetic modification cannot be regarded as a reliable denominator of risks and safety of the specific modifications in an individual plant. In addition, novelty or familiarity cannot serve as an overall indicator for certain groups of NGTs. Only a case-by-case analysis as performed under the current legislation can ensure a high safety level.

Directed mutagenesis techniques are new, with too little data and experience available to draw general conclusions about risk assessment. The current regulation in the EU is suitable for eliminating risks for humans and the environment for applications of genetic engineering, including directed mutagenesis and cisgenesis, as it guarantees a high safety level and ensures the application of the precautionary principle.

4.2 Integration of a sustainability analysis and proof of benefit for society

A binding sustainability analysis is based on established policies

Established international policies at the level of the CBD (e.g., Article 26 of the Cartagena Protocol on Biosafety) and the United Nations (SDGs) as well as the EU (most recently: European Green Deal, Farm to Fork Strategy, EU Sustainable Development Strategy) provide a **convincing basis for including a sustainability analysis** in the assessment of new technologies. With regard to assessments of GMO, there has been ongoing political and academic discourse about the possibilities for including sustainability aspects, although regulatory implementation has been rather sparse (Binimelis and Myhr, 2016).

Operationalisation of a binding sustainability analysis and proof of benefits

The Norwegian Gene Technology Act is an example of **how a sustainability assessment of GMO can be implemented** (Ref Act; see analysis by Myskja and Myhr, 2020, for its continued relevance specifically with regard to genome editing in plants). In EU GMO regulation, the relevance of sustainability criteria is reflected to some extent in Directive (EU) 2015/412, an amendment to the Release Directive (Directive 2001/18/EC Article 26b) which allows Member States to restrict GMO cultivation on policy grounds. However, taking this option into account is voluntary, and no guidance is included on the implementation of specific sustainability criteria. In order to improve this situation and **enable binding and well-devised implementation of sustainability criteria,** BfN is working on implementing a **technology assessment.** This integrated scientific assessment goes beyond current statutory risk assessment by taking into account **societal needs as reflected in the United Nations SDGs** and requiring **proof of benefit** to society or the environment. Investigating a benefit to society or the environment or a societal need (v. Calster et al., 2018), involves context characterisation, i.e., a description of the *status quo* with a view to how it is framed. The proof of benefit should also include an evaluation of alternative approaches to the assessment.

Legal foundation for a binding sustainability analysis and proof of benefit

The potential requirement for a verifiable benefit or contribution to the achievement of the sustainability policy would have to be in line with the requirements of the legal framework. Any framework for a sustainable food system needs to comply with binding legal principles. As a result, future legislation can include an assessment of whether plants and their products contribute to sustainability only within the clearly defined legal framework set by European law. In view of this, proof of benefit can thus only supplement the existing legal framework that ensures the safety of the environment and human health. The upstream verification of a specific benefit for a political policy must therefore – also in the interest of legal certainty – be carried out on the basis of legally predefined assessment steps based on scientific considerations, which enable an official decision that can be fully reviewed by the courts. The requirement for proof of benefit for GMO permissions would under these circumstances not be met with any concerns about compatibility with European fundamental rights or the requirements of WTO law (Spranger, 2021b, 2019).

Scope of the sustainability analysis and proof of benefit

With regard to the assessment of sustainability and benefit, it should be noted that these are **additional instruments aimed at strengthening the goals** of the European Green Deal and its Farm to Fork Strategy, the EU Sustainable Development Strategy and the United Nations SDGs. It is important that the precautionary principle be upheld to ensure that measures taken to implement

policies do not lead to results that contradict their fundamental aims. Only the safe use of new technologies like directed mutagenesis will enable the resulting opportunities to be fully harnessed and ensure their long-term use.

4.3 Further pillars of a viable framework for the future

Better implementation of the administrative framework

Procedural and organisational structures are important to ensure that legal regulations function. The best possible implementation of procedural precautions plays a central role, especially in technology law, because here preventive measures must be taken by making predictive decisions about possible future hazards. This idea is also recognised in European law under Art. 41 of the Charter of Fundamental Rights of the EU, which establishes a right to good administration. Administrative procedures for authorising projects with possible significant environmental impacts should therefore be designed to be as effective as possible.

Against this background, in addition to the sufficient resources of the administrations to be ensured by the Member States, it also appears necessary under European law to provide the envisaged external bodies, such as ethics committees (Art. 29 of Directive 2001/18/EC), with clearly defined procedural structures and a predefined and balanced set of appropriate experts. This would help manage the multi-layered discussions in society and increase the degree of transparency and thus serve as a basis for decision-making for the administration through transdisciplinary treatment (Spranger, 2021c).

Further specifications of legal liability

Moreover, the provision for legal liability for damages resulting from the use of GMOs could be a suitable subject to discuss in more detail. So far, European genetic engineering law only stipulates very general provisions on legal liability for individual damage. Art. 33 of Directive 2001/18/EC only requires Member States to determine the penalties applicable to breaches of the national provisions adopted pursuant to this Directive and to ensure that these penalties are effective, proportionate and dissuasive. It would be desirable and beneficial for the Europe-wide uniformity of the application of genetic engineering law if uniform specifications for strict and joint liability to protect those injured by GMO applications were to be established.

Enabling independent biosafety research

A more well-defined procedure for independent risk research and the amount of resources required for this research as well as specifications for enabling access to seed material are required to reach the objectives of the GMO legislation. Recital (21) of Directive 2001/18/EC stipulates that systematic and independent research on the potential risks involved in the deliberate release or the placing on the market of GMOs be conducted and that independent researchers be given access to all relevant material, while respecting intellectual property rights. Although many GMOs have been authorised and placed on the EU market, this requirement has not been fulfilled so far because researchers have been denied access to GM material including comparators to independently carry out meaningful research projects.

This weakness of GMO authorisation is important for at least two reasons. (i) It is a fundamental characteristic and prerequisite of science that the results it produces and the knowledge it generates can be verified. This presupposes that the material, i.e. the GMO and its comparator, is available.

Otherwise, the environmental risk assessment and the GMO authorisation process do not meet high scientific standards. (ii) According to the current GMO legislation, consent for the application of a GMO for placing onto the EU market shall not exceed ten years. Consent limited to a specific time period complies with the precautionary principle because it reflects that fact that any risk assessment – for a deliberate release according to part C of Directive 2001/18/EC – contains inherent uncertainties. One way to address these uncertainties when subsequently renewing authorisation is to consider *any other new information, which has become available on the risks of the product to human health and/or the environment*, i.e. during the first ten years. This requirement is only meaningful when independent research projects can be carried out to prove that the assumptions made in the initial environmental risk assessment apply.

Access to GMO material and the comparator therefore needs to be ensured in each case before consent for placing a GM plant or GM product on the market can be issued. The material should be kept by an independent body or institution under the direction of the Commission or one of its institutions to allow for independent research projects on the impacts of the GMO and the assumptions and benefit claims made.

An international GMO registry to improve detection and identification of GMOs in the EU

In order to identify and detect GMOs without authorisation, information on the genetic modification is crucial; this is true for all categories of genetic engineering from NGTs to transgenesis. The current system requires specific information that unauthorised GMOs are on the market in order to take action, i.e. develop a method to detect these events, in e.g. commodities. The current procedure is imperfect for all categories of GMOs as information frequently becomes known about unauthorised GMOs, which have been on the market for an unknown amount of time (e.g. see transgenic petunia). In order to improve the situation, an international database containing information on all GMOs would be desirable. A database of this kind could be implemented in the EU and different categories of information from the public domain (i.e. scientific literature and patents) could be entered, from application procedures in third countries and from (potential) applicants. A European project with a similar objective already exists in the EUginius database, which could serve as a starting point. Information from the Biosafety Clearing House and the OECD database could be integrated. We propose additionally ensuring sufficient resources in order to overcome current and future challenges for the detection, identification and quantification of GMOs on the European market.

Improved assessment of herbicide resistance

Long-term experience with the adoption of GM crops resistance to herbicides has shown that they negatively affect biodiversity. From this point of view, plants derived from directed mutagenesis and cisgenesis that are resistant to broad spectrum herbicides, a trait that is fairly easy to achieve, do not contribute to a sustainable agri-food system. As the tendency to stack resistance to different herbicides in GM crops is ongoing, it is particularly important to assess the impacts of the application of herbicide mixtures and their residues on health and the environment. As the authorisation of GM crops resistant to herbicides covers not only the GM crop, but also the use of complementary herbicides, the impacts mentioned must be assessed more effectively within GMO legislation. What also merits attention and needs to be adapted in the GMO legislation is that the herbicide applications for GM material used in studies must correspond to actual farming practices otherwise the GM material assessed will not be the same as the material that reaches the EU market. This will

strengthen the protection of health and environment and the trust of consumers in the GMO legislation.

5 Possible impacts and how to assess them

In the Inception Impact Assessment, the Commission presents the baseline scenario, followed by different elements for alternative policy options, which have not yet been developed. It is therefore difficult to fully identify and describe likely economic, social and environmental impacts at this stage.

As an alternative, we have provided a list below of the most important issues and criteria to consider for an impact assessment of different areas, once the various policy options have been fully developed and are available:

- Protecting and conserving biodiversity
- Protecting ecologically sensitive areas
- Ensuring that the precautionary principle is fully applied
- Ensuring that the polluter-pays principle is fully applied
- Respecting the requirements of the CBD including the Cartagena Protocol
- Ensuring that plants and products derived from directed mutagenesis and cisgenesis can be identified and detected
- Safeguarding the coexistence of different agri-food systems in terms of breeding, growing, trading and marketing
- Ensuring that the objective of the Farm to Fork Strategy that at least 25% of the EU's agricultural land will be used for organic farming by 2030 can be reached
- Assessing whether new mechanisms for benefit analysis comply with the science-based character of GMO authorisation
- Assessing the impact on present and prevailing agri-food sectors (conventional farming, organic farming) and their potential to mitigate or intensify societal challenges
- Protecting against the import of non-authorised plants and products derived from directed mutagenesis or cisgenesis
- Ensuring the freedom of choice for breeders, producers and consumers of plants and their products
- Assessing the societal challenges and the impact on the trust and acceptance of the public towards GMOs, NGTs and the EU legislation given how the legislative proposal is justified (timeliness, potential of NGTs, link to challenges etc.)

6 Relevant studies and literature

Agapito-Tenfen, S.Z., Okoli, A.S., Bernstein, M.J., Wikmark, O.-G., Myhr, A.I., 2018. Revisiting Risk Governance of GM Plants: The Need to Consider New and Emerging Gene-Editing Techniques. Frontiers in Plant Science 9, 1874. https://doi.org/10.3389/fpls.2018.01874.

Binimelis, R., Myhr, A.I., 2016. Inclusion and Implementation of Socio-Economic Considerations in GMO Regulations: Needs and Recommendations. Sustainability 8, 62. https://doi.org/10.3390/su8010062.

Biswas, S., Tian, J., Li, R., Chen, X., Luo, Z., Chen, M., Zhao, X., Zhang, D., Persson, S., Yuan, Z., Shi, J., 2020. Investigation of CRISPR/Cas9-induced SD1 rice mutants highlights the importance of molecular characterization in plant molecular breeding. Journal of Genetics and Genomics. https://doi.org/10.1016/j.jgg.2020.04.004.

Eckerstorfer, M.F., Engelhard, M., Heissenberger, A., Simon, S., Teichmann, H., 2019a. Plants Developed by New Genetic Modification Techniques – Comparison of Existing Regulatory Frameworks in the EU and Non-EU Countries. Frontiers in Bioengineering and Biotechnology 7, 26. https://doi.org/10.3389/fbioe.2019.00026.

Eckerstorfer, M.F., Grabowski, M., Lener, M., Engelhard, M., Simon, S., Dolezel, M., Heissenberger, A., Lüthi, C., 2021. Biosafety of Genome Editing Applications in Plant Breeding: Considerations for a Focused Case-Specific Risk Assessment in the EU. BioTech 10. https://doi.org/10.3390/biotech10030010.

Eckerstorfer, M.F., Heissenberger, A., Reichenbecher, W., Steinbrecher, R.A., Waßmann, F., 2019b. An EU Perspective on Biosafety Considerations for Plants Developed by Genome Editing and Other New Genetic Modification Techniques (nGMs). Frontiers in Bioengineering and Biotechnology 7, 319. https://doi.org/10.3389/fbioe.2019.00031.

EFSA Panel on Genetically Modified Organisms, 2010. Guidance on the environmental risk assessment of genetically modified plants. EFSA Journal 8, 1879. https://doi.org/10.2903/j.efsa.2010.1879.

EFSA Panel on Genetically Modified Organisms, 2012a. Scientific opinion addressing the safety assessment of plants developed through cisgenesis and intragenesis. EFSA Journal 10, 2561. https://doi.org/10.2903/j.efsa.2012.2561.

EFSA Panel on Genetically Modified Organisms, 2012b. Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function. EFSA Journal 10. https://doi.org/10.2903/j.efsa.2012.2943.

EFSA Panel on Genetically Modified Organisms, 2020. Applicability of the EFSA Opinion on site-directed nucleases type 3 for the safety assessment of plants developed using site-directed nucleases type 1 and 2 and oligonucleotide-directed mutagenesis. EFSA Journal 18, 1611. https://doi.org/10.2903/j.efsa.2020.6299.

EFSA Panel on Genetically Modified Organisms, 2021. Evaluation of existing guidelines for their adequacy for the molecular characterisation and environmental risk assessment of genetically modified plants obtained through synthetic biology. EFSA Journal 19. https://doi.org/10.2903/j.efsa.2021.6301.

European Commission, 2021a. Study on the status of new genomic techniques under Union law and in light of the Court of Justice ruling in Case C-528/16. COMMISSION STAFF WORKING DOCUMENT SWD(2021) 92 final, Brussels. https://ec.europa.eu/food/plants/genetically-modified-organisms/new-techniques-biotechnology/ec-study-new-genomic-techniques_en (accessed 11 October 2021).

European Commission, 2021b. Legislation for plants produced by certain new genomic techniques. Legislative Proposal Ref. Ares(2021)5835503, Brussels. https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques_en (accessed 1 October 2021).

GGSC - Gaßner, Groth, Siederer & Coll., 2018. EuGH-Urteil zur Mutagenese: Auswirkungen auf die Kennzeichnung "Ohne Gentechnik". http://www.ohnegentechnik.org/fileadmin/ohne-gentechnik/dokumente/downloads/180725_GGSC_Stellungnahme_zum_EuGH-Urteil_zur_Mutagenese.pdf (accessed 11 October 2021).

Kawall, K., 2019. New Possibilities on the Horizon: Genome Editing Makes the Whole Genome Accessible for Changes. Frontiers in Plant Science 10, 280. https://doi.org/10.3389/fpls.2019.00525.

Kawall, K., 2021. Genome-edited *Camelina sativa* with a unique fatty acid content and its potential impact on ecosystems. Environmental Sciences Europe 33. https://doi.org/10.1186/s12302-021-00482-2.

Massel, K., Lam, Y., Wong, A.C.S., Hickey, L.T., Borrell, A.K., Godwin, I.D., 2021. Hotter, drier, CRISPR: the latest edit on climate change. Theoretical and Applied Genetics. https://doi.org/10.1007/s00122-020-03764-0.

Myskja, B.K., Myhr, A.I., 2020. Non-safety Assessments of Genome-Edited Organisms: Should They be Included in Regulation? Science and engineering ethics. https://doi.org/10.1007/s11948-020-00222-4.

Nabel, M., Selig, C., Gundlach, J., Decken, v. d., H., Klein, M., Jessel, B., 2021. Bodenreport: Vielfältiges Bodenleben – Grundlage für Naturschutz und nachhaltige Landwirtschaft. BfN, Bonn, 54 pp. https://www.bfn.de/fileadmin/BfN/landwirtschaft/Dokumente/210108_BodenBioDiv-Report.pdf (accessed 11 October 2021).

Parisi, C., Rodríguez-Cerezo, E., 2021. Current and future market applications of new genomic techniques, Luxembourg, 52 pp. https://publications.jrc.ec.europa.eu/repository/bitstream/JRC123830/210419_ngt_market_study_final.pdf.

Ribarits, A., Eckerstorfer, M., Simon, S., Stepanek, W., 2021a. Genome-Edited Plants: Opportunities and Challenges for an Anticipatory Detection and Identification Framework. Foods (Basel, Switzerland) 10, 430. https://doi.org/10.3390/foods10020430.

Ribarits, A., Narendja, F., Stepanek, W., Hochegger, R., 2021b. Detection Methods Fit-for-Purpose in Enforcement Control of Genetically Modified Plants Produced with Novel Genomic Techniques (NGTs). Agronomy 11, 61. https://doi.org/10.3390/agronomy11010061.

Ricroch, A.E., Martin-Laffon, J., Rault, B., Pallares, V.C., Kuntz, M., 2021. Next biotechnological plants for addressing global challenges: The contribution of transgenesis and new breeding techniques. New biotechnology. https://doi.org/10.1016/j.nbt.2021.09.001.

Schulz, R., Bub, S., Petschick, L.L., Stehle, S., Wolfram, J., 2021. Applied pesticide toxicity shifts toward plants and invertebrates, even in GM crops. Science 372, 81–84. https://doi.org/10.1126/science.abe1148.

Schütte, G., Eckerstorfer, M., Rastelli, V., Reichenbecher, W., Restrepo-Vassalli, S., Ruohonen-Lehto, M., Wuest Saucy, A.-G., Mertens, M., 2017. Herbicide resistance and biodiversity: agronomic and environmental aspects of genetically modified herbicide-resistant plants. Environmental Sciences Europe 29, 5. https://doi.org/10.1186/s12302-016-0100-y.

Selig, C., Gundlach, J., Decken, v. d., H., Nabel, M., Klein, M., Jessel, B., 2021. Handlungserfordernisse zur Ausgestaltung des nationalen GAP-Strategieplans: Positionspapier. BfN, Bonn, 18 pp.

https://www.bfn.de/fileadmin/BfN/landwirtschaft/Dokumente/20210108_Positionspapier_GAP2023.pdf (accessed 11 October 2021).

Spranger, T.M., 2017. In-depth analysis of various European directives and regulations with regard to their potential to regulate environmental effects of New Technologies besides Genetic Engineering Law. Im Auftrag des Bundesamtes für Naturschutz. https://www.bfn.de/fileadmin/BfN/recht/Dokumente/NT_Auffangrechte_RGutachten_Spranger_en.pdf (accessed 11 October 2021).

Spranger, T.M., 2019. Memorandum on the question of the world trade law implications of the European Court of Justice's judgment in Case C-528/16. Im Auftrag des Bundesamtes für Naturschutz. https://www.bfn.de/fileadmin/BfN/recht/Dokumente/Spranger_int_trade_law_implications_C528_16.pdf (accessed 11 October 2021).

Spranger, T.M., 2021a. Gutachterliche Stellungnahme zum Themenkomplex Nachweis von GVO als Voraussetzung für die Regulierung. Im Auftrag des Bundesamtes für Naturschutz. https://www.bfn.de/fileadmin/BfN/recht/Dokumente/Gentechnikrecht/Gutachterliche-Stellungnahme-zum-Themenkomplex-Nachweis-von-GVO-als-Voraussetzung-fuer-die-Regulierung.pdf (accessed 11 October 2021).

Spranger, T.M., 2021b. Gutachterliche Stellungnahme zum Themenkomplex Nutzennachweis. Im Auftrag des Bundesamtes für Naturschutz. https://www.bfn.de/fileadmin/BfN/recht/Dokumente/Gentechnikrecht/Gutachterliche-Stellungnahme-zum-Themenkomplex-Nutzennachweis.pdf (accessed 11 October 2021).

Spranger, T.M., 2021c. Gutachterliche Stellungnahme zum Themenkomplex Verfahrensmäßige Vorkehrungen. Im Auftrag des Bundesamtes für Naturschutz. https://www.bfn.de/fileadmin/BfN/recht/Dokumente/Gentechnikrecht/Gutachterliche-Stellungnahme-zum-Themenkomplex-Verfahrensmaessige-Vorkehrungen.pdf (accessed 11 October 2021).

v. Calster, G., Garnett, K., Reins, L., 2018. On a need to have basis: the innovation principle, the rule of law and EU regulation on new technologies - A Research Agenda. Environmental Law & Management 30, 10–13.

v. d. Decken, H., Jessel, B., Krug, A., Schuster, B., Stratmann, U., 2017. Agriculture Report 2017: Biological diversity in agricultural landscapes. Agrarreport. BfN, Bonn, 66 pp. https://www.bfn.de/fileadmin/BfN/landwirtschaft/Dokumente/Agriculture_Report_2017.pdf (accessed 11 October 2021).

Zsögön, A., Cermak, T., Voytas, D., Peres, L.E.P., 2017. Genome editing as a tool to achieve the crop ideotype and *de novo* domestication of wild relatives: Case study in tomato. Plant Science 256, 120–130. https://doi.org/10.1016/j.plantsci.2016.12.012.