

Testbiotech analysis of the EU Commission’s Inception Impact Assessment on “Legislation for plants produced by certain new genomic techniques”, published 24 September 2021



Testbiotech e. V.
Institute for Independent
Impact Assessment in
Biotechnology

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Summary

The European Commission published its Inception Impact Assessment on “Legislation for plants produced by certain new genomic techniques” (EU Commission, 2021a) on 24 September 2021. It is based on its previous staff working document regarding the status of new genomic techniques under EU law (EU Commission, 2021b).

While officially calling for adequate regulation and high safety standards, the EU Commission seems in reality to be following a different strategy: the document appears to indicate an intention and plans for far reaching deregulation of plants derived from new genetic engineering (New GE). Risks associated with the processes of New GE are either not given sufficient weight or are completely disregarded. Neither is the complexity of New GE applications sufficiently represented.

The Commission is further ignoring the huge technical potential of tools, such as CRISPR/Cas gene scissors, to cause new and specific risks. Both the intended alterations and the unintended effects can differ extensively from those resulting from non-targeted mutagenesis and conventional crossing. Therefore, no conclusions on the general safety of plants derived from the processes of New GE can be drawn without carrying out detailed risk assessment or a ‘product-based risk assessment’. Neither is it sufficient to simply consider the intended traits.

Consequently, the published document is likely to misinform and misdirect the further discussions. The Commission is in danger of proposing new EU regulation which is not sufficiently based on science, but driven by the interests of industry and other stakeholders with an interest in the application and marketing of these technologies and products.

In addition, the Commission's document also ignores the successes, the flexibility and the advantages of current EU regulation. Likewise, it disregards the need to improve risk assessment of transgenic plants.

It goes without saying that the Commission should develop its position to be non-biased and evidence-based. On this basis, the Commission should correct its assumptions and begin an appropriate process for a fact-finding mission.

1. New and specific risks of plants derived from New GE

New GE is a collective term for a number of biotechnological tools, the most prominent of which are site-directed nucleases (SDNs) such as the gene scissors CRISPR/Cas. New GE can induce a wide range of different alterations at the targeted regions of plant genomes, ranging from single point mutations to very complex changes (e.g. altering multiple genes simultaneously or introducing transgenes). These technologies can, but do not necessarily, introduce new genetic information from other species. They can, however, result in diverse mutations causing specific patterns of genetic alterations (i.e. genotypes) that can lead to new traits (i.e. phenotypes) which may go beyond what is achievable with conventional breeding, and which can escape the boundaries of genome organisation that naturally restrict the outcome of conventional breeding (Kawall, 2019).

For example, Bt toxins in plants only occur if the plants are transgenic, and the same is true for many genotypes and phenotypes in plants derived from New GE. This is also the case even if no additional genes are inserted, as evidenced by examples such as wheat which is supposed to produce less gluten (Sánchez-Leon et al., 2018) or less acrylamid (Raffan et al., 2021), tomatoes with increased GABA content (Nonaka et al., 2017) and camelina with changes in oil composition (see Kawall, 2021).

The intended traits in the plants mentioned above are associated with specific risks for consumers (e.g. production of new proteins/peptides or other changes in plant composition) as well as for farming (e.g. increased susceptibility to plant diseases or plant pests) and the environment (e.g. disruption of food webs or interspecies communication).

Importantly, the risks of New GE application in plants are not only caused by the intended traits, but also by the technical processes: for example, in most cases, one of the first steps in New GE includes using older genetic engineering techniques to insert the DNA for the gene scissors into the plant cells. These non-targeted methods (such as 'gene gun' and usage of *Agrobacterium tumefaciens*) are known to induce unintended alterations in the plant genome or epigenome (Forsbach et al., 2003; Gelvin, 2017; Jupe et al., 2019; Liu et al., 2019; Makarevitch et al., 2003; Windels et al., 2003).

In addition, the action of the gene scissors may be imprecise, e.g. cutting at wrong sites on the genome or unintentionally inserting additional DNA, thus causing the unforeseen production of new biologically active molecules (such as proteins or RNAs) or unintentional interference in gene regulation. These undesirable effects arising from the technical process may occur at the target site or at other sites on the genome ('off-target') (see, for example, Biswas et al., 2020; Kapahnke et al., 2016; Kosicki et al., 2018; Lalonde et al., 2017; Höijer, et al., 2021), and can be very different to spontaneous alterations in the genome. The reason: similarly to the intended effects, the undesirable effects can escape the boundaries of natural genome organisation (Testbiotech 2021b, Eckerstorfer et al., 2021; Kawall et al., 2020).

In summary, it could be said that there is no such thing as a ‘free lunch’: the huge technical potential of tools, such as CRISPR/Cas gene scissors, also causes new and specific risks. Both the intended alterations and the unintended effects can differ extensively to those which may be caused by non-targeted mutagenesis and conventional crossings. Therefore, no general conclusions can be drawn on the safety of plants derived from the processes of New GE without detailed risk assessment. It certainly cannot be concluded simply by considering the intended traits.

2. How the Commission is preparing for deregulation

By focusing on the intended traits, the EU Commission is creating the impression there are whole groups of plants derived from New GE that could be exempt from mandatory risk assessment. In paving the way for this deregulation, the Commission refers to EFSA, and has made four basic statements:

(1) *“Among NGTs, targeted mutagenesis and cisgenesis can be used to produce alterations of the genetic material that can also be obtained by natural mutations or conventional breeding techniques.”*

This statement basically is correct. It is true that, by using tools such as CRISPR/Cas, mutations can be obtained that are known from conventional breeding. For example, it can be seen from patent applications that CRISPR/Cas is used to imitate genetic alterations derived from non-targeted mutagenesis and conventional crossings, and thus to extend the scope of the patents (Testbiotech, 2021a). If these patents are granted, they cover both the plants derived from conventional breeding and plants derived from New GE. They can then be used to seriously hamper or block access to the biological material needed by other breeders. Therefore, the scope of such patents must be restricted to specific technical processes to ensure freedom to operate for conventional breeders.

Quite apart from the above strategy of companies to use New GE to extend their monopolistic proprietary control over conventional breeding, it is, in addition, not plausible that the companies are mainly interested in imitating genotypes that could also be derived from conventional breeding. On the contrary, industry is eager to use New GE techniques to generate genotypes and phenotypes that go beyond what is achievable with non-targeted mutagenesis and conventional crossing. Therefore, it should be clarified that although the type of alterations (i.e. point mutations, small insertions, deletions etc) induced by New GE and conventional breeding techniques are similar in nature, this is not necessarily the case for their exact position on the genome or their combinations (see also Testbiotech, 2021b).

(2) *“The European Food Safety Authority (EFSA) concluded that plants obtained by targeted mutagenesis and cisgenesis can have the same risk profile as plants produced with conventional breeding.”*

This statement is rather misleading: first of all, on the basis of the technical processes used in the New GE applications described above, there are no general categories of plants that can be exempted from mandatory risk assessment because they display the ‘same risk profile’ as conventional breeding (Eckerstorfer et al., 2021; Kawall et al., 2020). Rather, the risks can only be assessed by looking at each individual application, case by case, taking into account the technical process used (including unintended effects) and the characteristics of the product.

This also applies to cisgenesis, as the example of hornless cattle shows: New GE was used in this case to transfer a gene from one cattle breed to another. It was meant to be a gene transfer within the same species, i.e. cisgenesis. As a result, some calves were born without horns, and these in turn gave birth to a following generation of calves, again with no horns. The hornless cattle were proudly presented by the University of California. However, as more detailed analysis showed, the process used to introduce the genes had serious consequences: it was shown that bacterial genes, including genes for resistance to antibiotics, were also inserted into the genome of the cattle. As a result, the cattle were found to be transgenic, but not cisgenic (Norris et al. 2020). This was only noticed after several years and the animals had to be killed. If these animals had been used for further breeding, thousands of cattle and hundreds of farmers breeding the cattle could have been affected. This once again shows that even cisgenesis (no matter whether in plants or animals) requires thorough risk assessment, taking into account the unintended effects caused by the technical processes. It is simply not sufficient to only assess the intended trait.

Furthermore, it should be acknowledged that EFSA did not have a mandate to examine the full range of risks arising from New GE processes. Instead, EFSA only had a mandate to assess whether the current framework for risk assessment as used for transgenic crops could also be applied to plants derived from New GE. Therefore, the EFSA opinion (2020) cannot be used to conclude on general statements such as those made by the Commission. In addition, EFSA has still not conducted a systematic scientific literature screening to examine the full range of risk associated with the application of New GE in plants (see also Testbiotech, 2021b).

Finally, EFSA findings are still not clear. In its report published in 2020, EFSA comes to the conclusion that current risk assessment may also be sufficient for crops derived from New GE (EFSA, 2020). However, in their report from 2021 (which is not mentioned by the EU Commission), EFSA refers to a low-gluten wheat developed by Sánchez-Leon et al., 2018 (EFSA, 2021). They come to the conclusion that, due to complex genetic alterations, new risk assessment approaches might be needed. EFSA calls these Synbio approaches: „(...) *the large number of mutations required to achieve gluten-free wheat is far beyond any plant previously assessed. This is likely to require SynBio approaches to correctly identify all gliadins and glutenins in the hexaploid genome of bread wheat and to identify an engineering strategy that introduced mutations of the correct nature and positions in each gene to prevent the accumulation of any peptide fragments associated with initiation of the inflammatory cascade.*“

(3) *“These techniques can be used to produce alterations of the genetic material that can also be obtained by natural mutations and conventional breeding techniques, or can be used to produce alterations that are more complex.”*

If the above explanations are taken into account, this statement may at first sight appear to be correct because it shows that, even without insertion of additional DNA, the genotypes and phenotypes of the plants derived from New GE can go beyond what is achieved with conventional breeding. However, it is also likely to lead to a serious misunderstanding: it creates the impression that the necessity for risk assessment can be decided simply by knowing about the intended traits (which may be more complex), leaving aside the unintended effects caused by the technical processes (see above).

(4) *“Current regulatory oversight and requirements, however, are not adapted to the resulting diverse risk profiles, and in some cases can be disproportionate or inadequate.”*

Again, this statement is somewhat misleading. While it is true that all organisms derived from genetic engineering techniques have to undergo risk assessment, it is not true that all GE organisms are assessed in the same way. Rather, as the existing EFSA opinions on risk assessment of transgenic plants show, different traits (such as insect toxicity, herbicide tolerance, intended drought tolerance or changes in oil composition), deserve specific data which also guide the design of the field trials, the toxicity studies and the overall risk assessment. Therefore, the existing system already provides substantial flexibility.

There are further misleading concluding remarks in the Commission document:

(5) *“EFSA has concluded that plants produced by targeted mutagenesis and cisgenesis generally pose lower risks than plants obtained with conventional genetic modification techniques (transgenesis). However, they are subject to the same requirements”*

As explained, EFSA (2020) did not have a mandate to draw up a report on the full range of risks. On the contrary, EFSA (2020) stated that no comprehensive review of existing publications was carried out. Therefore, the assumption of the EU Commission is not supported by a mandate and the findings of EFSA (2020) and, in addition, ignores the findings of EFSA’s opinion from 2021.

Furthermore, by defining transgenesis as ‘conventional’ genetic modification techniques, the Commission seems to be implying that transgenic plants produced by previous methods should be regarded as ‘conventional’ and may, therefore, be exempted from regulation in the future (Testbiotech, 2021c). In doing so, the Commission is choosing to ignore the need to substantially improve the risk assessment of transgenic crops (Testbiotech 2021d).

(6) *“In addition, EFSA also concluded that, in some cases, plants produced by targeted mutagenesis and cisgenesis do not pose new hazards compared to plants produced with classical mutagenesis or conventional breeding techniques.”*

This finding needs to be elucidated: it shows that EFSA also assumes that there are other cases of New GE plants associated with new and specific risks (hazards). In these other cases, plants derived from New GE may not obviously show new risks, but they can nevertheless have risks that are already known and need to be assessed. Therefore, no conclusions on the safety of the plants derived from New GE can be drawn without risk assessment of intended and unintended effects. This statement nicely illustrates the one-sided presentation of the issues. Overall, the Commission’s text does not address the risks and complexity, but instead emphasises the safety and innovation of New GE applications.

(7) *“Furthermore, the GMO Panel considers that the existing Guidance for risk assessment of food and feed from genetically modified plants and the Guidance on the environmental risk assessment of genetically modified plants are sufficient but are only partially applicable to plants generated via SDN-1, SDN-2 or ODM. Indeed, those guidance documents’ requirements that are linked to the presence of exogenous DNA are not relevant for the risk assessment of plants developed via SDN-1, SDN-2 or ODM approaches if the genome of the final product does not contain exogenous DNA.”*

This statement is basically correct. However, it cannot be used to justify the need for a change in GMO regulation. As explained above, the current system already provides sufficient flexibility to

address these differences. It also should be taken into account, that some applications of New GE will also need risk assessment methodology that goes beyond existing guidance (EFSA, 2021).

Thus, while the EU Commission claims that their initiative will maintain the objectives of the current legislation in regard to a high level of protection for human and animal health and the environment, at the same time, the published document is paving the way for many plants derived from New GE to be exempt from existing regulation. Consequently, the initiative, if implemented, would result in a lowering of existing environmental and health standards.

3. What about the potential benefits of New GE?

In comparison to the risks, the EU Commission strongly emphasises the potential benefits:

“The study has also concluded that plants obtained from NGTs have the potential to contribute to the objectives of the European Green Deal and in particular to the Farm to Fork and Biodiversity Strategies and the United Nations’ Sustainable Development Goals (SDGs) for a more resilient and sustainable agri-food system. Examples of potential benefits include plants more resistant to pests, diseases and environmental conditions or to the effects of climate change (e.g. droughts), or requiring less natural resources and fertilisers. NGTs could also improve the nutrient content of plants for healthier diets, or reduce content of harmful substances such as toxins and allergens.”

Testbiotech agrees that New GE and tools such as CRISPR/Cas have an impressive technical potential. However, in regard to the goals of the Green Deal, the Farm to Fork and Biodiversity Strategies as well as the SDG goals, this potential needs a critical appraisal.

Firstly, the introduction of transgenic plants more than two decades ago came with similar promises. Despite the fact that these promises and expectations have not materialised (see, for example, Schulz et al., 2021), industry is still trying to uphold these narratives. Thus, before claiming that New GE could solve problems in regard to biodiversity, sustainable agriculture and climate change, there first of all needs to be a detailed assessment of experience gained from GE plants already on the market.

Secondly, in regard to biodiversity, sustainable agriculture and climate change, there is no doubt that, amongst other things, greenhouse gas emissions due to human activity are putting increasing pressure on ecosystems and biodiversity. Invasive species, pests and pathogens are endangering biodiversity and food security. More extreme weather conditions, including drought, flooding and cold, are already endangering many regions. As a result, biodiversity, ecosystems and agriculture will undergo rapid changes and suffer serious damage. In many cases, the environment is already adversely impacted by other human activities, and climate change is causing additional stress, leading to potential tipping points in the ongoing extinction of many species.

What is the role that genetically engineered plants might play in this context? Could we, for example, use New GE to create plants that are tolerant to various environmental stressors just in time? Can we protect biodiversity and safeguard food security by designing, for example, trees with an ‘optimised’ genome? And, in addition, should we erase less advantageous species with techniques such as gene drives?

Evolution builds on genetic and biological diversity which, as a system, can continue to evolve, very often using already existing solutions to problems. It is not simply about the single ‘fittest’ organism to survive, but about populations and ecosystems which are diverse and flexible enough to

respond to new environmental conditions. For example, it has been shown that honey bees and pollinated plants can evolve together and survive conditions arising from climate change in a kind of orchestrated process of development (Bartomeus et al. 2011).

The speed of climate change caused by human activity is generally considered to go beyond anything that the natural world has ever been exposed to over millions of years. On the other hand, research carried out on plants shows that many species have an amazing potential to adapt and co-evolve in changing environmental conditions, also using epigenetic mechanisms. In addition, genetic diversity within species and ecological networks is key to providing a sufficiently broad range of possible solutions to the upcoming new problems. Against this backdrop, there is an abundance of scientific evidence in support of strategies aiming to increase diversity in agroecology systems (GIZ, 2020). The same is true for forests (see for example Morin et al., 2018) and grasslands (see for example Isbell et al., 2015).

Genetically engineered plants, on the other hand, may promote evolutionary mismatch-effects within such complex systems, which may, in turn, interrupt finely-tuned interactions between the species and the dynamics of co-evolution. For example, a disturbance has been shown in the interactions between genetically engineered cotton and correlated ant species. This is likely to foster the spread of Bt cotton in biodiversity hotspots (Vázquez-Barrios et al., 2021).

We should agree that we are not cleverer than evolution. The potential releases of genetically engineered organisms to combat or mitigate climate change appear to be driven mostly by particular interests, and are not suited to providing adequate solutions. We should not put our faith in false hopes: if we do not stop climate change, no technology will ever be able to prevent the extinction of thousands of species. And it will not provide us with miracle plants that will safeguard our daily lives in a biosphere which is out of balance.

4. Flexibility and benefits within current system should be acknowledged

The Commission document voices a lot of criticism regarding the current regulatory system. It states that the current legislation would no longer be fit for purpose. This statement is closely aligned to the perspective of those stakeholders with an economic interest in rapid market access for New GE products.

At the same time, the Commission completely omits any mention of the benefits of the current system. A much more comprehensive analysis of its strengths and weaknesses is needed, taking into account a sufficiently broad range of different perspectives.

Taking a closer look at the document reveals further issues in regard to the Commission's reasoning:

- For example, despite legal clarification provided by the EU Court of Justice ruling (Case C-528/16), the Commission claims that legal uncertainties in Directive 2001/18/EC (and other legislation based on it) have been compounded by New GE developments.
- Despite the substantial flexibility within the current system (see above), it is claimed that current regulatory oversight and requirements cannot be adapted to a diversity of risk profiles.

- Despite many experts agreeing that identification and traceability of the plants derived from New GE are feasible if the relevant information is provided by the applicant, the Commission appears to doubt whether the current system of traceability can be implemented in future.
- Finally, while EU Directive 2001/18 already enables the risk manager to assess potential benefits, societal challenges and sustainability criteria (see, for example, Recital 62 of Directive 2001/18), the Commission is proposing the new introduction of such mechanisms. In light of this demand, it is astonishing that the Commission did not use existing regulatory in last 20 years.

In addition, the benefits, such as transparency, safeguarding consumer choice and enabling organic agriculture to develop its markets, are not mentioned by the Commission as positive outcomes of current EU regulations. This is even more surprising given the Commission's commitments under the Farm-to-Fork-Strategy to a) increase the area used for organic farming, and b) provide more transparency for consumers in the food sector. Furthermore, it also should be acknowledged that so far, the uncontrolled spread of GE plants (as has been observed in the US, Canada, Australia, Japan and Mexico) has mostly been prevented in the EU because of existing mechanisms in current regulations.

It is astonishing that the Commission has failed to emphasise the successes of existing EU legislation. The current GMO regulation puts the EU in an advantageous position in comparison to other regions. It is, therefore, hard to understand why this legislation should now be abandoned in the face of the emergence of powerful New GE techniques that should be subjected to continuous and comprehensive oversight as a matter of increasing urgency.

5. Summary

The stakes are high. Especially when confronted with rapid technological developments and insufficient regulation of New GE, which is likely to lead to:

- › serious damage to biological diversity;
- › the introduction of risks in food production that may accumulate unnoticed;
- › no access to data needed for risk assessment by independent experts since it is not made available;
- › no measures being available to stop the uncontrolled spread of the organisms in the environment;
- › no data being available to track and trace the New GE organisms and products derived thereof;
- › agriculture and food production no longer being able to rely on GE free sources being protected.

The Commission should undoubtedly develop its position to be unbiased and evidence-based. Therefore, the Commission should correct its assumptions and start to engage in an appropriate process for a fact-finding mission.

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