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The future regulation of NGT plants: Questions that still need to be answered

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Introduction

The European Commission published its proposal for the future regulation of plants obtained from new genomic techniques (NGT) in July 2023. In February and April 2024, the EU Parliament adopted a position that differs substantially from the Commission proposal. The Council, during the Spanish and Belgian Presidency, has been discussing so far without coming to a common position. In May 2024, the Belgian Presidency made a new proposal for a common position. However, many open questions remain.

There are three main issues that complicate the discussion:

- The risks of NGT plants: the French authority ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail) published two detailed reports, which were particularly critical of the criteria for Category 1 NGT plants as proposed by the Commission. Furthermore they showed substantial differences in risks arising from NGT plants as compared to plants obtained from conventional breeding. A specific decision making tree for approval processes is suggested (ANSES, 2023 & 2024). These reports add to concerns as also raised by other experts and national agencies (for overview see: Testbiotech, 2024a).

- Impact on consumers and non-GE food production: labeling, choice and transparency for consumers, farmers and food producers were a main matter of concern of the EU

Parliament. In result, the Parliament voted in favor of food labeling, contrary to the proposal of the EU Commission.

- Access for breeders: the EU Parliament, as well as many EU Member States, requested that no patents should be granted on NGT plants.

The following section provides a short overview and attempts to identify the most relevant issues that need to be resolved in order to achieve a scientifically based, transparent and sustainable future regulation of NGT plants. The questions raised are relevant not only for the protection of health and environment or the interests of the broader public: legal clarity is also needed for stakeholders who want to introduce NGT plants (and products derived thereof) into the Common Market. If the safe handling of such products is not guaranteed by the legal framework, their introduction may create massive problems for future generations, including economic damages and irreversible harm to biodiversity. Further prominent concerns are market disturbances, the disruption of innovation in plant breeding and damage to the interests of consumers.

1. Examining the relevant differences between conventional breeding (including random mutagenesis) and NGT-plants

Several well documented cases show that NGT plants which are unlikely to be obtained from conventional breeding methods (including random mutagenesis)[1] would be equated to conventionally bred plants by the proposed future regulation and thus escape risk assessment.

These include

- 'GABA-tomato' (Nonaka et al., 2018)
- oil producing camelina (Morineau et al., 2017)
- rice with changes in protein content (Wakasa et al., 2024)
- poplar with very early first flowering (Ortega et al., 2022)
- switchgrass with higher tillering (Yang et al., 2018).

In addition, there are specific NGT approaches which aim to make the plant genome more widely available for changes beyond the limits of conventional breeding:

- One example are knock-outs of small, but very powerful regulatory units known as miRNA. It is known that these interventions can cause profound changes in plant development, plant architecture and plants' response to the environment (for summary see: Testbiotech, 2024b). It is known that these genetic changes are practically impossible to achieve using conventional breeding methods.

[1]For the purposes of this backgrounder, the term 'conventional methods' is defined as previously established processes used in plant breeding with the following characteristics: conventional breeding which is dependent on material with high genetic diversity. It is only in a second step (ex-post) that the trait is developed from this material. Random mutagenesis using physical and chemical triggers is included in this definition, as it aims to increase genetic diversity in the plant material used for the selection of traits. In contrast, genetic engineering methods (old and new) can be used to insert a new trait directly into a plant genome, independently of the genetic diversity that is present in a given plant material. These profound technical differences between processes of conventional breeding and methods of genetic engineering could also be used to introduce a definition for conventional breeding which is absent in the current proposals (see ANSES 2024).

- Further examples are the breaking up of genetic linkages and gene clusters or the knocking out of larger gene families, – again almost impossible to achieve using previous breeding methods (see for example Kawall, 2021a).
- Another example are re-arrangements of larger parts of chromosomes (such as deletions or inversions) which are introduced intentionally (Rönspies et al., 2021) or may be unintended (Samach et al., 2023; Liu et al., 2023) that are hardly seen from plants obtained by conventional breeding (ANSES, 2024). These changes can cause profound changes in the genomic architecture of the plants and may destabilize genomic functions to large extent. Some authors have even speculated that new plant species could emerge from this approach (Rönspies et al., 2021).

In summary, applications that (i) profoundly alter the biology of plants and (ii) result in traits of NGT plants that go beyond the known biological characteristics of existing species or (iii) possibly may constitute new plant species, can escape mandatory risk assessment if the proposals by the Commission or Parliament would be adopted.

Therefore, the question arises as to whether findings from recent case studies (not assessed by EFSA) can be integrated into the debate on the future regulation of NGT plants in order to strengthen its scientific basis. The answer to this question is highly relevant for the regulation of NGT plants since these differences are also associated with specific risks (see below).

2. Applying case-specific risk assessment

As the report from ANSES (2023) shows, the overall number of genetic changes or the length of the sequence of substituted nucleotides are not related to the risks of NGT plants. Therefore, the formal criteria as proposed by Commission or Parliament are not sufficient to draw any conclusions on the safety of NGT plants.

In a second report, ANSES (2024) provides an overview on risks related to the intended traits of NGT plants. Preliminary risk analysis was derived from twelve case studies of NGT plants. As ANSES shows, the likelihood of the mutations occurring at a specific site or in specific combinations are especially relevant in this context (see above). It is concluded that some of the plants will require further in-depth risk assessment and that some of the identified risks are relevant for several cases (see Table 1).

Furthermore, ANSES (2024) also gives examples of unintended genetic changes and argue that they should also be taken into account in risk assessment. If unintended genetic changes were to remain undetected for several years, the plants may be widely cultivated and propagated over longer periods of time, before undesirable effects get noticed. Apart from risks for health and the environment, this also would carry high financial risks for food producers and farmers.

ANSES thus clearly identifies the need for a case-by-case risk assessment. The question arises as to how to integrate these findings, which have not been taken into account by EFSA, into future regulation of NGT plants in order to protect health and the environment.

Table 1: Health and environmental risks associated with plants derived from site-directed mutagenesis and identified in case studies (source: ANSES, 2024, non-official translation).

	Risks identified	Case studies
Comparative assessment, plant composition	Pleiotropic effects leading to a change in the plant's agro-phenotypic properties or composition. In the case of multiplexing or if a transcription factor is targeted, increased risks associated with pleiotropic effects.	Herbicide-resistant potatoes Gluten-reduced wheat
Toxicity, allergenicity, nutritional assessment	In the event of a change in composition, whether desired or unexpected, or a potential change in the toxicity, allergenicity or nutritional characteristics of the plant.	Tomato with high GABA (γ-aminobutyic acid) content
Environmental risks	Risk of gene flow from edited genes to wild or cultivated populations If a growing number of modified species are cultivated, there is an increased risk of gene transfer to weed species, including invasive species. Modification of interactions with animals consuming plants obtained using NTGs and with insect pollinators. Changes in selection pressure could lead to an increase in the pathogenicity of certain biological hazards, particularly for long-lived crops. In the case of multiplexing, transfer of gene combinations with unassessed epistasis.	Tomato with high GABA content Rice with reduced size Sage with reduced phenolic acid content Grape resistant to *Botrytis cinerea* Switchgrass with increased tillering

3. Avoiding the worst case for the ecosystems

There are specific concerns about NGTs being applied in populations of wild and non-domesticated (or only partially domesticated) plants (GFÖ, 2023). Relevant cases include grasses (Yang et al., 2018), medical plants (Zhou et al., 2018) and trees (Ortega et al., 2022), as well as the de-novo domestication of wild species (Zsögön et al., 2018). There are similar concerns regarding NGT plants belonging to domesticated species that are able to persist and spread in the environment, or even cause gene flow to other, non-domesticate species (Koller et al., 2023).

These applications share a high risk of uncontrolled spread and also unexpected and potentially harmful next generations effects (Bauer-Panksus et al., 2020). Losing spatio-temporal control on NGT plants and allowing them to 'go wild' would mean exposing ecosystems to long-term, non-predictable and multifaceted risks without having any effective measures in place to intervene, in case something goes wrong.

Another worst case for ecosystems may emerge from the speed of development and the scale of releases of NGT organisms that are not well adapted to the ecosystems. There are reasons for concern that the resilience of the receiving environments may become overstretched and some tipping points may be reached which do not allow to restore the ecosystem functions after a 'breakdown' (Koller et al., 2023).

Future regulation should take these worst case scenarios for the ecosystems and biodiversity into account. There is a clear need for the introduction of cut-off criteria and defined limits to possible release of NGT plants. Furthermore, it is crucial that not only the risks of specific events should be subjected to mandatory risk assessment, but also the overall impact, exposure and scale of releases for the receiving environments is taken into account. For example, in the case of NGT brassicaceae oil plants, their potential to spread and cross as well as their possible negative impact on pollinators will largely depend on the scale of their releases (Koller et al., 2024).

The proposal of the Belgian Presidency does not solve the problem: It includes all plant species that are used for planting. This would include trees, grasses, medical plants, *de-novo* domesticated plants and arable plant species that can persist and spread in the environment.

The question needs to be answered about what is needed in the future regulation of NGT plants to allow the risk manager to monitor the scale of releases and, if required, to control, limit or reduce them.

4. Developing an integrated regulatory approach

The idea of Commission and Parliament is to introduce new legislation that is adapted to the technical specificity of NGT plants. There is consensus that NGTs are more targeted than the old GE methods. It is also known that NGTs can generate traits that go beyond what can be expected from conventional breeding or what is known from the biological characteristics of existing species. At the same time, all experts agree that the field of technology will evolve further. For example, it is thought that Artificial Intelligence (AI) will significantly boost developments.

Currently, we do not have a clear picture about the specific risks of NGT plants and how they should be assessed. It also remains to be seen in future, which and how many traits may become relevant for releases.

Therefore, instead of creating new legislation for NGTs that is based only on the current state of technology, which may soon be outdated, it would be better to develop regulation that can be adapted smoothly and allows the risk manager to have oversight and control in an expanding field.

ANSES (2024) proposes a decision tree that works within current regulation, but which is able to adapt current risk assessment to the evolving field of NGT plants (see Figure 1). Step by step risk assessment can actually speed up decision-making if there are no indications of reasons for concern in the first stages. The applicant still has to provide some data, but the overall amount of data requested could be significantly reduced. Therefore, this decision tree corresponds to the intentions of the Commission and the Parliament to simplify the approval process for lower risk NGT plants.

At the same time, the regulation would still allow the political decision-maker to oversee and monitor the scale of releases. The most controversial points of transparency, coexistence and consumer choice could remain regulated as they are, but could also be combined with additional information.

The question that needs to be answered is how to arrive at a sustainable legal framework that can be adapted to the evolving field of NGT plants, but which is based on the precautionary principle and open to future developments. In this regard, the ANSES (2024) report follows the idea of the Commission and the Parliament without ‘throwing out the baby with the bathwater’.

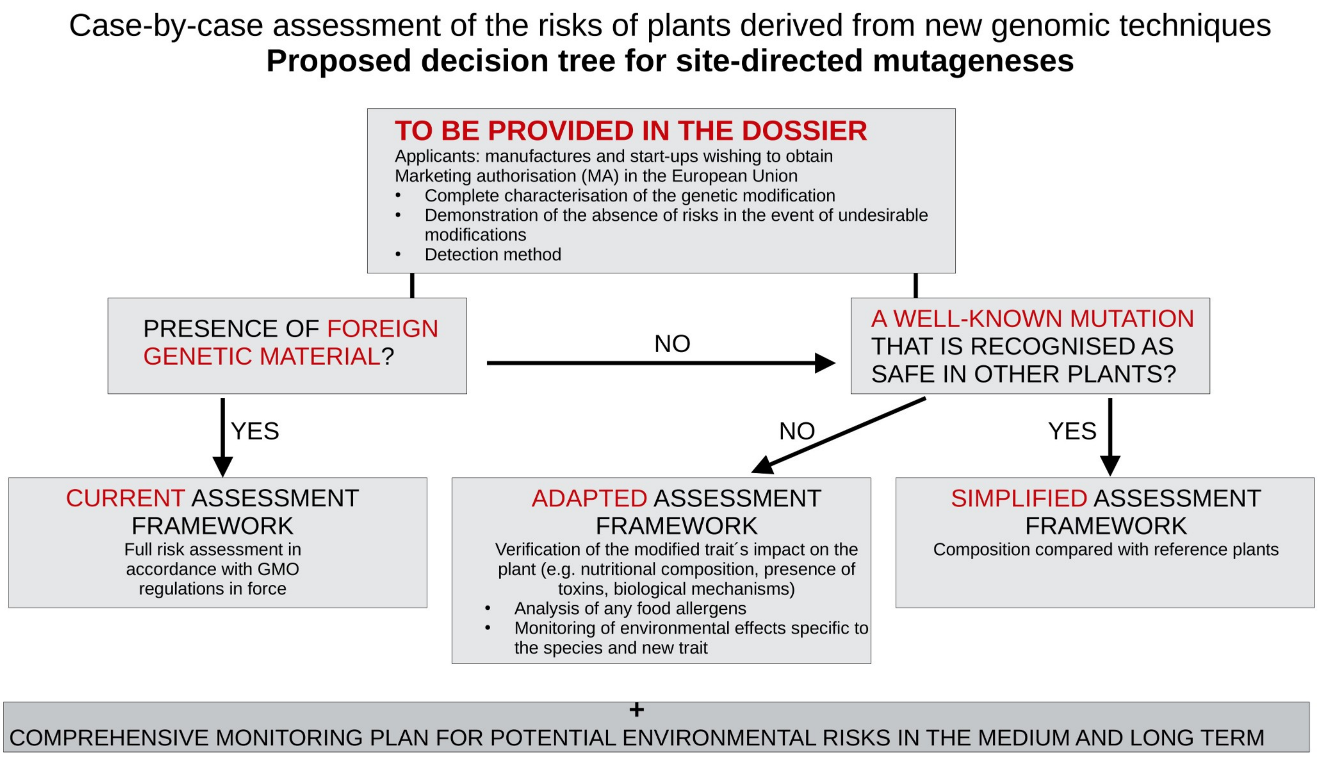

Figure 1: Decision tree for assessing the health and environmental risks of plants derived from site-directed mutagenesis using a CRISPR-Cas system (source: ANSES, 2024, non-official translation)

5. Organising access to biological resources needed for plant breeding

The Parliament hopes that the EU will ban patents on NGT plants. According to the proposed regulation, some NGT plants would be equated to conventionally-bred plants (Category 1) and, therefore, not patentable. However, this hope is very likely to fail, as GMO regulation has nothing to do with patent law. NGT plants are patentable in the EU, even if they do not have to be tested for risks. All 39 contracting states of the European Patent Office (EPO) would have to agree before patents on genetically engineered plants could actually be banned. This approach is being blocked by industry, patent attorneys and several EPO contracting states.

However, to keep the freedom to operate for European breeders (known as breeders' privilege), the EU would now have to clarify that, as long as patents on seeds are not prohibited completely, only genetically engineered plants can be patented. Therefore patents granted on NGT plants could not be expanded to plants derived from other methods.

The Belgian Presidency proposes to allow NGT plants to be categorized as 'Category 1' only if no patents are filed on it. This idea appears to be used as 'selling point' to introduce NGT plant categories that would escape mandatory risk assessment. Such 'deals' mix risk assessment with patent law and should be treated with great caution. In addition, the problem with patents granted on conventionally-bred plants would remain. Currently, more than 1000 conventionally-bred varieties are already affected by patents. This problem would not be solved if the 'deal' were to be accepted. Under these circumstances, it cannot be excluded that the proposed regulation could simply be circumvented: The companies may now claim that (some) of the plants are derived from random mutagenesis. The EPO's current practice would allow such patents (see No Patents on Seeds!, 2024).

The question needs to be answered, what can be done to safeguard access to biological resources and biodiversity needed by all breeders, even if no solution can yet be found to prohibit patents on NGT plants.

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