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How to ensure a science-based and up-to-date regulation of NGT plants

Quick reading: Summary of findings and recommendations for the EU Commission proposal regarding NGT plants and their risk assessment

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The problem with Category 1
The EU Commission proposal for the future regulation of NGT plants introduces criteria and categories which have no precedent. These criteria are not science-based, but rather an expression of obscure and formal measures. If adopted, they would allow far-reaching irreversible decisions to be made, with huge consequences for future generations. We estimate that more than 90% of NGT applications in plants would be declared equivalent to conventional plants under Category 1, thereby being exempted from risk assessment. According to the criteria, NGT plants could be legally equated to conventionally-bred plants even if they show significant biological differences.

What are the most relevant differences between NGT plants and conventional breeding?
The EU Commission refers to EFSA advice in order to justify its approach, but the Commission never asked EFSA the decisive question: What are the relevant differences between NGTs and conventional breeding in regard to risk assessment? This may have been one reason why EFSA 'overlooked' the most relevant differences: For example, by introducing only minor nucleotide changes, CRISPR/Cas gene scissors have the potential to alter gene functions and plant characteristics in ways that would not be expected with conventional breeding. In result, the plants obtained from NGTs, even those that would fall in Category 1, can escape the boundaries of traits specific to individual species. Therefore, risks to health and the environment cannot be regarded as generally lower in comparison to transgenic plants.

Criteria are based on inadequate assumptions
The EU Commission published a backgrounder (Council of the European Union, 14204/23, Interinstitutional File: 2023/0226(COD), Brussels, 16 October 2023)[1] to justify the criteria included in Category 1: "The criteria were developed to define type and number of mutations introduced by targeted mutagenesis and cisgenesis that could also be obtained by conventional breeding methods or could occur spontaneously." (emphasis added) This statement from the Commission clearly shows that its criteria do not address the relevant differences between NGT plants and conventional breeding:

Evidence of flaws in Category 1: The number and type of genetic changes
The crucial factor when comparing NGT plants and conventional breeding is not the type and number of mutations, but rather the sites and the functions of the altered genes. In many cases, the resulting traits could not have been obtained using conventional breeding. The reason: NGT

[1] https://data.consilium.europa.eu/doc/document/ST-14204-2023-INIT/EN/pdf

processes can overcome critical limitations in conventional breeding (see, for example, Kawall, 2019).

Evidence of flaws in Category 1: The number of mutations and nucleotides
Many publications show that intended NGT effects (below 20 genetic changes, involving less than 20 nucleotides each) can result in genotypes and phenotypes that are unlikely to occur in conventional breeding (see for example Kawall, 2021a; Nonaka et al., 2017). Therefore, it is not sufficient to simply count the number of mutations; their biological effects must also be assessed.

Evidence of flaws in Category 1: The deletion and inversion sites
Recent studies show that NGT interventions can cause unintended inversions and deletions at specific genomic sites which would be unlikely to occur in conventional breeding (Liu et al., 2023; Samach et al., 2023, Koller & Cieslak, 2023). Therefore, the effects of deletions and inversions caused by NGT processes have to be assessed before any conclusion can be reached on the safety of the plants derived thereof.

Evidence of flaws in Category 1: The breeders' 'virtual' gene pool
Recent studies show that unintended genetic interactions (epistasis) may occur if gene variants are introduced into plants from the same species, i. e. belonging to the same 'gene pool' but with different 'genetic backgrounds'. For example, a gene introduced into the genome of a Peruvian wild type tomato may have a very different effect if it is introduced into a tomato previously bred in Europe (Alonge et al., 2020; Aguirre et al., 2023; Kawall, 2021b; Koller et al., 2023). Therefore, if genes are transferred within a (virtual) breeders' gene pool, neither the absence of unintended effects nor the safety of NGT plants can be concluded without risk assessment.

Irreversible decision-making based on flawed criteria
According to Category 1, NGT plants that are clearly biologically different in regard to their genotype and phenotype would, nevertheless, be legally equated to conventionally-bred plants. Therefore, decisions based upon these criteria (and their potential consequences) would be irreversible. There would be no requirement for tracking or tracing; specific monitoring would likewise not be requested for these plants or their offspring. Neither would there be any measures required to enable coexistence or prevent environmental spread and gene flow. Even non-domesticated species (such as weedy plants, grasses, forest trees) that are able to persist, reproduce and spread in the environment could become Category 1 NGT plants.

Possible solutions to Category 1 problems
If Category 1 NGT plants are to be introduced into regulation, robust scientific standards will be necessary to verify whether they really can be regarded as similar to conventionally-bred plants. In order to do this, the plants should be first subjected to an 'in-door risk assessment' that requires experiments under contained conditions: the 'in-door risk assessment' should consist of steps such as molecular characterisation (identification of (un-) intended genetic changes and the effects they may cause), bioinformatics, 'omics' and exposure to defined stressors in the greenhouse (or climate chamber).

Proportional risk assessment: The 'best of two worlds'
The suggested steps in risk assessment (above) are proportional and to some extent already part of internal quality checks of the companies. If an 'in-door risk assessment' does not show significant differences compared to conventionally-bred plants, further steps in risk assessment, such as field trials, may be obsolete. Category 1 NGT plants (and products) would not be equated to conventionally-bred plants, and thus allow specific monitoring, coexistence procedures as well as

the withdrawal of market approval if necessary. The current system is sufficiently flexible and would allow the introduction of an ‘in-door risk assessment’.

Category 2: Risk assessment
The risk assessment of Category 2 NGT plants should be carried out in accordance with the current regulations. It should be performed on a case-by-case basis. There should be no categorisation into ‘risk profiles’ which would allow risk assessment to be reduced to the intended effects of the final product. Intended and unintended genetic changes and the effects that go along with it have first to be assessed before decision are taken on the further steps in risk assessment.

Precautionary principle
As far as the precautionary principle is concerned, specific provisions should be introduced in regard to spatio-temporal control. This should help to avoid uncontrolled spread or gene flow, and would be essential for the assessment of cumulative and long-term effects.

Systemic effects and scale of releases
The release of several NGT plants with different traits into a shared environment would necessitate the establishment of clear criteria and methodologies to assess potential interactions and cumulative effects. This would be required to avoid disruption of ecosystem processes by organisms which have not been adapted to existing biodiversity (Koller et al., 2023). Similar to climate change, it is the speed of developments that can overstretch the resilience of the ecosystems. The introduction of measures to control and limit the overall scale of releases in terms of the number of organisms and traits would be vitally important.

Summary
The EU Commission proposal cannot ensure health or environmental safety if NGT plants or products derived thereof are released into the environment, or are placed on the EU market. Therefore, the current proposal should be rejected or extensively revised.

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