ZKBS
The Central Committee on Biological Safety

Ref. 45310.0121 October 2023

Position Statement of the ZKBS on the European Commission's proposal for a regulation on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation (EU) 2017/625

INITIAL SITUATION

According to a decision of the European Court of Justice of 25 July 2018, plants bred with certain new genomic techniques (e.g. CRISPR/Cas9) ("NGT plants") are considered genetically modified organisms (GMOs) [under Directive 2001/18/EU]. They are, therefore, regulated as strictly as classical GMOs, e.g. organisms containing genes from sexually not compatible species.

On 30 April 2021, the European Commission published a study showing that the present regulation is not fit for purpose: It does not reflect the lower risk potential of NGT plants [1]. Furthermore, NGT plants offer opportunities for the EU's goal of developing a more sustainable agriculture. In addition, a number of non-EU countries have exempted NGT plants from regulation under genetic engineering law, with the result that numerous improved crops have been realised there and the first modified plants have been placed on the market already. The present EU regulation on GMOs requests an identification technique for NGT plants, which is technically not implementable for most cases.

PROPOSAL OF THE EUROPEAN COMMISSION

The European Commission published a proposal for the new regulation of NGT plants on 5 July 2023 [2]. According to this proposal, there is no "opt-out" of individual member states, i.e. these regulations should apply EU-wide. The regulations apply to all plant species including macroalgae. In brief, the following categories of NGT plants are proposed:

NGT-1: NGT plants with certain genetic modifications (point mutations, insertions of up to 20 nt or contiguous DNA sequences of any length from the breeder's gene pool, any deletions, inversions) will not be regulated under present European GMO legislation in future. Food, feed and other products derived from these plants will not be labelled. Seeds, on the other hand, must be labelled. A public register will be set up listing NGT plants together with their modifications in order to allow breeders and growers to recognise them. The number of such changes in the genome is limited to 20.

NGT-2: NGT plants with genetic modifications that are not considered NGT-1 plants remain within the regulatory scope of genetic engineering law and are decided on them occurs on a case-by-case basis.

POSITION STATEMENT OF THE ZKBS

General assessment of the proposal

The ZKBS welcomes the initiative of the European Commission for an adapted regulation of plants bred with new genomic techniques.

The present restrictive regulation does not reflect the current scientific knowledge, as plants bred with NGT (e.g. genome editing using CRISPR/Cas9) typically contain genetic modifications that can also arise naturally or through classical breeding methods (including cross-breeding and mutagenesis breeding). In the view of the ZKBS and other national surveillance and (law) enforcement authorities as well as the EFSA (European Food Safety Authority), such NGT plants therefore do not pose an increased risk compared to classically bred plants [3].

The new regulation proposes that NGT plants, whose genetic modifications could also result from natural processes or classical breeding methods (NGT-1), are legally considered to be on the same level as classically bred plants and are exempt from GMO regulation. This proposal follows the practice of those countries where such plants are already not regulated as GMOs, such as the USA, Canada, Japan and Argentina. Worldwide, after less than 10 years, there are already hundreds of examples of NGT plants, including a large number with beneficial properties. The use of NGT makes breeding approaches faster, more precise and it saves resources and, hence, it can contribute to the EU goal of rendering agriculture more sustainable.

The ZKBS expects that, in case of a possible application of NGT techniques in wild plants, the conservation biological objectives laid down in international and national regulations (e.g. CBD, Directive 43/92/EEC, BNatSchG §40) will be maintained and the use of the potential of wild plants for crop breeding will remain unaffected by the new regulation.

In detail, the ZKBS wishes to raise attention to following comments

1. Insertion size

The limit proposed by the Commission for the insertion of any sequence is a length of 20 inserted nucleotides (NGT-1), which reflects an earlier ZKBS Position Statement [4]. Insertions of this size occur frequently naturally for instance in global representatives of *Arabidopsis thaliana* [5]. However, recent genome comparisons of crop plants having larger genomes also show a significantly larger variation of their genomes. In the sequenced genomes of 101 wild and cultivated plants from the species barley, potato, soybean and tomato, more than 3 million sequence changes exceeding 50 nucleotides in length were discovered, with many extending over 1000 nucleotides or more [6–10]. On the basis of the frequent natural insertions of 20 or more nucleotides in the genomes of plants, it is apparent for the ZKBS that there is no immediate increase in risk associated with increasing insertion size.

The proposed limit of 20 inserted nucleotides is understood to be of a technical nature in order to achieve a legally definable and thus applicable demarcation from more complex alterations,

which could also be produced with the new genomic techniques. However, on the basis of the new findings on genome research, a limit of 20 nucleotides is scientifically outdated. A procedure to adjust this limit to accommodate in the future the ever-growing understanding of plant genomes, is necessary.

2. Maximum number of changes

The Commission's decision to set a maximum number of 20 changes per plant raises a number of questions.

1. The maximum number of 20 targeted changes in an NGT-1 plant is very small compared to thousands of random changes in the genome after classical mutagenesis breeding. These mutagenesis-derived plants are exempt from GMO regulation though.
2. According to the European Commission, a cross between two NGT-1 plants should also be considered an NGT-1 plant, even if the maximum number of 20 changes is exceeded. The European Commission does not see any increase in risk in exceeding the maximum number of 20; this safety assessment is shared by the ZKBS. Ultimately, this challenges the definition of a maximum number of changes.
3. The ZKBS shares the view that the number of changes must be related to the haplotype of a plant, i.e. it is independent of the ploidy level of a plant. This should be phrased more clearly. In the opinion of the ZKBS, the haplotype of a plant must also include the haplotypes of plastids and mitochondria. This should also be anchored in the draft by the European Commission.
4. According to the Commission's proposal, the maximum of 20 changes includes all changes in bioinformatically predictable regions in the genome. However, for two reasons, such potential non-target events should not be included in the count of alterations.
   a) These regions cannot be defined without prior accurate knowledge of the genome sequence or pangenome. Such information is not available for many plant species at present, but could become known later with the consequence that legal uncertainties could arise.
   b) Such non-target events occur rarely in NGTs, especially compared to classical non-targeted mutagenesis breeding.

With this Position Statement, the ZKBS aims to contribute to a clarification of the proposed law in order to make it legally secure and future-proof.

REFERENCES

1. **European Commission** (2021). EC study on new genomic techniques. 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 https://food.ec.europa.eu/plants/genetically-modified-organisms/new-techniques-biotechnology/ec-study-new-genomic-techniques_en. Visited on 11.10.2023.

2. **European Commission** (2023). New techniques in biotechnology. Proposal for a REGULATION OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL on plants obtained by certain new genomic techniques and their food and feed, and amending Regulation

(EU) 2017/625 https://food.ec.europa.eu/plants/genetically-modified-organisms/new-techniques-biotechnology_en. Visited on 11.10.2023.

3. **Paraskevopoulos K, Federici S** (2021). Overview of EFSA and European national authorities' scientific opinions on the risk assessment of plants developed through New Genomic Techniques. *EFSA J* **19**(4):e06314.

4. **Zentrale Kommission für die Biologische Sicherheit** (2012). Stellungnahme der ZKBS zu neuen Techniken für die Pflanzenzüchtung. (Az. 402.45310.0104).

5. **Cao J, Schneeberger K, Ossowski S, Günther T, Bender S, Fitz J, Koenig D, Lanz C, Stegle O, Lippert C, Wang X, Ott F, Müller J, Alonso-Blanco C, Borgwardt K, Schmid KJ, Weigel D** (2011). Whole-genome sequencing of multiple *Arabidopsis thaliana* populations. *Nat Genet* **43**(10):956–63.

6. **Jayakodi M, Padmarasu S, Haberer G, Bonthala VS, Gundlach H, Monat C, Lux T, Kamal N, Lang D, Himmelbach A, Ens J, Zhang X-Q, Angessa TT, Zhou G, Tan C, Hill C, Wang P, Schreiber M, Boston LB, Plott C, Jenkins J, Guo Y, Fiebig A, Budak H, Xu D, Zhang J, Wang C, Grimwood J, Schmutz J, Guo G, Zhang G, Mochida K, Hirayama T, Sato K, Chalmers KJ, Langridge P, Waugh R, Pozniak CJ, Scholz U, Mayer KFX, Spannagl M, Li C, Mascher M, Stein N** (2020). The barley pan-genome reveals the hidden legacy of mutation breeding. *Nature* **588**(7837):284–9.

7. **Tang D, Jia Y, Zhang J, Li H, Cheng L, Wang P, Bao Z, Liu Z, Feng S, Zhu X, Li D, Zhu G, Wang H, Zhou Y, Zhou Y, Bryan GJ, Buell CR, Zhang C, Huang S** (2022). Genome evolution and diversity of wild and cultivated potatoes. *Nature* **606**(7914):535–41.

8. **Liu Y, Du H, Li P, Shen Y, Peng H, Liu S, Zhou G-A, Zhang H, Liu Z, Shi M, Huang X, Li Y, Zhang M, Wang Z, Zhu B, Han B, Liang C, Tian Z** (2020). Pan-Genome of Wild and Cultivated Soybeans. *Cell* **182**(1):162-176.e13.

9. **Gui S, Wei W, Jiang C, Luo J, Chen L, Wu S, Li W, Wang Y, Li S, Yang N, Li Q, Fernie AR, Yan J** (2022). A pan-*Zea* genome map for enhancing maize improvement. *Genome Biol* **23**(1):178.

10. **Li N, He Q, Wang J, Wang B, Zhao J, Huang S, Yang T, Tang Y, Yang S, Aisimutuola P, Xu R, Hu J, Jia C, Ma K, Li Z, Jiang F, Gao J, Lan H, Zhou Y, Zhang X, Huang S, Fei Z, Wang H, Li H, Yu Q** (2023). Super-pangenome analyses highlight genomic diversity and structural variation across wild and cultivated tomato species. *Nat Genet* **55**(5):852–60.

Statement of the ZKBS on the Proposal of the European Commission for the new regulation of plants produced by New Genomic Techniques (NGT)

Minority vote, October 2023

Dr. Elisabeth Bücking, Sölden

There are passages in the statement I do not agree with

1. The statement refers to „the scientific view of the ZKBS, of other national surveilling authorities and of the EFSA“ as evidence, that NGT-plants pose no higher risk than conventional plants. These assessments, however, could not take into account more recent publications – the EFSA assessment was published in 2021 (see ref. 3 of the statement). More recent studies definitely indicate higher risks if NGT are applied to plants, cf.

CRISPR/Cas9-induced DNA breaks trigger crossover, chromosomal loss, and chromothripsis-like rearrangements, A. Samach et al., *The Plant Cell*, 27 July 2023
https://doi.org/10.1093/plcell/koad209

2. One difficulty of the new jurisdiction is to determine, how the equivalence to conventional plants can be defined. This is crucial, since plants with this equivalence are classified as NGT-1 and exempted from the current GMO regulation: there will be no risk assessment and no general labeling. For this purpose a threshold shall be introduced in the proposed regulation for the number of acceptable nucleotide deviations. This threshold is not scientifically, but legally based. Such a threshold cannot be justifed scientifically, in principle, since there exists no rule, according to which few genotype deviations lead to minor and more genotype deviations to greater changes in phenotype. How the phenotype - that is the characteristics of a plant and its potential ecological risks - is affected depends on the location and the context of the genotypic deviations. That means, that one essential possibility to identify NGT-1 plants does not exist. It follows, that the category NGT-1 should be omitted.

3. Point 4. in the section „Maximum number of changes“ indicates, that in the view of the ZKBS it should be possible to apply NGT, even when the plant genome is not entirely sequenced. This I cannot accept. Analysis methodology is developing quickly; it would mean to reject this progress and to renounce the possibility to verify the absence of risk.

4. In preparing the statement it was extensively discussed, whether a section on „Wild Plants“ should be added with the aim of limiting the new regulation to crop plants. Wild plants are broadly connected ecologically. If subjected to NGT – which leads to new geno- and phenotypes – and eventually released, more biodiversity loss can be expected (see minority vote Prof. Katja Tielbörger). I regret, that such a section was not included. The reference to „international and national regulations“ and „the goals of nature conservation stipulated therein“, that „should remain unaffected by the new regulation“ cannot replace this section.

Minority vote on the opinion of the ZKBS on the proposal of the European Commission to re-regulate plants bred using "New Genomic Techniques (NGT)".

September 2023

Prof. Dr. Katja Tielbörger, University of Tübingen, Germany

Substantiation: The views presented therein are not fully shared by all working group members

Vote:

1) Most important point:

The EU Commission proposal explicitly refers to 'all plant species', i.e. potentially 300 000 plant species globally (Mora et al. 2011). Animals and microorganisms are excluded on the grounds that there is insufficient knowledge about these groups of organisms.

Expanding the category of NGT-1 plants to include all plants, i.e., even those not used for agriculture, is extremely problematic from the perspective of ecological and conservation biology science. These scientific findings (see below) are neither considered in the draft of the EU Commission nor in the ZKBS statement.

The introduction of new genetic material into a natural population will inevitably lead to outcrossing with plants in the wild population. This may have, among others, the following negative consequences:

On the one hand, **'outbreeding depression'** can occur (e.g. Montalvo & Ellstrand 2001), i.e. detrimental alleles can spread in the population, thus endangering its survival. Given the current burning biodiversity crisis, this risk is inacceptable.

The introduction of new genotypes into natural populations and communities can also cause the **new genotypes to rapidly multiply and spread**, endangering entire species communities. We furthermore know from invasion biology that this risk increases rapidly with the number of new genotypes or species introduced (Lockwood et al. 2009). Given the large numbers of new genotypes that can be expected to be created by NGT, this risk is also problematic in the age of extinction.

For these reasons, even intraspecific relocations of plants and animals are prohibited in international (e.g., Biodiversity Convention) or national (e.g., §40 paragr. 2 sentence 3 BNatSchG) regulations, or require careful risk analysis, e.g., in the context of restoration measures with non-regional seeds (e.g., Breed et al. 2013). Measures such as 'assisted migration' in the age of climate change are also highly controversially discussed in the scientific literature (e.g. Hamilton

2001, Ricciardi & Simberloff 2009) for the above reasons, and also because their effectiveness is highly debated (e.g. Bucharová et al. 2016, Gomez et al. 2015).

Thus, a regulation that classifies NGT-1 plants as 'quasi-natural', thus allowing their release into wild populations, would pose irreversible risks for the environment, nature, and species conservation, and possibly also create conflicts with existing legal regulations.

Furthermore, the assumption that more is known about all wild plants than about animals and microorganisms lacks a scientific basis. This statement can only be understood if the Commission's draft is meant to address solely cultivated plants.

In fact, there is **no visible benefit for nature conservation** and species protection, because the paper of the EU Commission as well as all preparatory papers are very clearly focused on crop plants in the agricultural sector. The extension of the NGT rules to wild plants thus appears not only risky but entirely unnecessary for the Commission to achieve their goal. Therefore, **the precautionary principle should apply**, and the application of NGT plants to wild populations should be subject to careful risk assessment. That is, the NGT-1 category should not apply to all plant species and especially not to wild plants.

2) Further point:

One difficulty with new regulation is determining how to define equivalence to classically bred plants. This is crucial because such apparently ‘natural’ plants classified as NGT-1 plants are exempted from regulation under the genetic engineering law, and thus from risk assessment and labelling.

In the draft, an arbitrary threshold for the number of modified nucleotides and places in the genome was selected. This refers to a single publication with a single species (Cao et al. 2011).

Such a threshold also appears to be difficult to justify scientifically, since there is no law according to which a few modifications in the genotype cause minor changes, while more modifications cause greater changes in the phenotype. However, the risk to conservation and species protection is caused by the phenotype, as well as the location and context of the genotypic modifications, and not on a specific number of genetic changes.

It follows that a major means of identifying NGT-1 plants is not applicable. A logical consequence would be to abandon the NGT-1 category altogether.

REFERENCES

Breed MF, MG Stead, KM Ottewell, *et al.* 2013: Which provenance and where? Seed sourcing strategies for revegetation in a changing environment. Conservation Genetics 14: 1-10.

Bucharová A, W Durka, JM Hermann, *et al*. 2016: Plants adapted to warmer climate do not outperform regional plants during a natural heat wave. Ecology & Evolution 6: 4160-4165.

Cao J. *et al*. 2011: Whole-genome sequencing of multiple *Arabidopsis thaliana* populations. Nature Genetics 43: 956-963.

Gomez *et al*. 2015: The silent extinction: climate change and the potential hybridization-mediated extinction of endemic high-mountain plants. Biodiversity Conservation 24:1843–1857.

Hamilton NRS 2001: Is local provenance important in habitat creation? A reply. Journal of Applied Ecology 38: 1374–1376

Lockwood JL, Cassey P, Blackburn TM. 2009. The more you introduce the more you get: the role of colonization pressure and propagule pressure in invasion ecology. Diversity and Distributions 15: 904-910

Montalvo AM, NC Ellstrand NC 2001: Nonlocal transplantation and outbreeding depression in the subshrub *Lotus scoparius* (Fabaceae). American Journal of Botany 88: 258-269.

Mora C, DP Tittensor, S Adl, AG Simpson, B Worm 2011: How many species are there on Earth and in the ocean? PLoS Biology 9: e1001127.

Ricciardi A, D Simberloff 2009: Assisted colonization is not a viable conservation strategy. Trends in Ecology and Evolution 24: 248-253