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European Food Safety Authority

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.

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COST Action CA18111 - Plant genome editing – a technology with transformative potential (PlantEd)

Public Consultation 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.

* Select the chapters you want to comment

- [x] Abstract
- [ ] Keywords
- [x] 1. Introduction
- [ ] 2. Data and Methodologies
- [x] 3. Assessment
- [x] 4. Conclusions
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- [x] 6. Reference
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Abstract

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PlantEd agrees with and wishes to emphasize the main finding of the EFSA Panel on Genetically Modified Organisms which could not find any new hazards specifically linked to the genomic modification produced via SDN-1, SDN-2 and ODM as compared to both SDN-3 and conventional breeding. Applying the precautionary principle as developed in the Commission's Communication (COM/2000/0001) and in European Court's case law and EU legislation, we trust that this is an important indication for the evaluation that the Commission is conducting in response to the Council's requests (Council Decision (EU) 2019/1904). Furthermore, PlantEd also agrees that the considerations relating to the introduction of a transgene, in 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 not relevant for the risk assessment of plants developed via SDN-1, SDN-2, and ODM approaches in case the genome of the final product does not contain exogenous DNA.

1. Introduction

- [x] 1.1 Background as provided by the European Commission
- [ ] 1.2 Background as provided by EFSA
- [x] 1.3 Terms of reference

1.1 Background as provided by the European Commission

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L. 77: The objective of Directive 2001/18/EC “is to approximate the laws, regulations and administrative provisions of the Member States and to protect human health and the environment when carrying out the deliberate release into the environment of genetically modified organisms for any other purposes than placing on the market within the Community, [and] placing on the market genetically modified organisms as or in products within the Community.” We suggest the sentence concerned to be rephrased in order to capture the complete intention of Directive 2001/18/EC.

L. 84/85: PlantEd suggests rephrasing line 86 as follows to further clarify what is referred to by conventional mutation breeding techniques: “…the EFSA GMO Panel considered in vivo and in vitro mutation breeding techniques that emerged before the…” The clarification should implement the European Court of Justice’s interpretation of the term “mutagenesis” in the Directive to exclude those methods/technologies developed primarily after 2001 ” (for a discussion of the Court ruling, see Purnhagen et al, 2018; Vives-Vallés and Collonnier, 2020).

1.3 Terms of reference

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Regarding Terms of Reference 1 (ToR1), PlantEd notes the following:

After the Judgment of the CJEU in case C-528/16, in line with the GMO Panel (that “did not identify any additional hazard associated to the use of the SDN-1, SDN-2 and ODM approaches as compared to both SDN-3 and conventional breeding techniques, including conventional mutagenesis” (EFSA, 2020: 12)), EFSA (2012) “is only partially applicable to SDN-1, SDN-2, and ODM, and may from a strictly scientific perspective not be relevant to the same”;

Therefore, PlantEd encourages EFSA to remain as consistent as possible in its scientific approach, while acknowledging the dilemmas that may result from the implementation of recent legal interpretations such as that of the CJEU in case C-528/16.

PlantEd invites the EFSA GMO Panel to exercise the proportionality test (a general principle of EU law) in a wider way that reflects more the reality of balancing the different (potential) impacts and to place greater emphasis on case-by-case evaluation. PlantEd considers EFSA’s mandate to ensure that all measures adopted do not go beyond what is necessary to achieve the goal stipulated by its mandate.

3. Assessment

- ☐ 3.1 Introduction - no text
- ☑ 3.1.1 Definition of gene editing: SDN 1, SDN-2, and ODM compared to SDN 3
- ☐ 3.1.2 Technology used in SDN 1, SDN 2, and ODM applications
- ☐ 3.1.3 Methods for delivering or expressing SDN in plants
- ☐ 3.2 ToR1 of the mandate: Applicability of the Section 4 of the EFSA opinion on SDN 3 to plants obtained using SDN 1, SDN 2 and ODM approaches - no text
- ☐ 3.2.1 Introduction
- ☐ 3.2.2 Assessment of Section 4 of the EFSA opinion on SDN 3 - no text
- ☐ 3.2.2.1 Assessment of section 4.1: Source of genes and safety of gene products
- ☐ 3.2.2.2 Assessment of Section 4.2: Alteration to the genome - no text
- ☐ 3.2.2.2.1 Alteration at the insertion site [Section 4.2.1]
- ☑ 3.2.2.2.2 Alteration elsewhere in the genome [Section 4.2.2]

3.3 ToR2 of the mandate: Applicability of the Conclusions of the EFSA opinion on SDN 3 to plants obtained using SDN 1, SDN 2 and ODM approaches

3.1.1 Definition of gene editing: SDN 1, SDN-2, and ODM compared to SDN 3

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L. 253: We suggest to broaden the sentence on the possibility of vegetatively propagated crops crossings, in the following way: “This step is, though possible, not routinely carried out in non-sexually propagated crops (such as vegetatively propagated crops).”

Figure on page 8: EFSA is correct in stating that “SDN-1, SDN-2, and ODM approaches differ from SDN-3 and transgenesis in that they do not result in the insertion of any transgene but rather in the modification of an already existing endogenous sequence.” However, PlantEd holds that the statement can be strengthened by alluding to the source and nature of the exogenous DNA as relevant as well. The figure also needs a correction: (1) at the top of the middle column: "No if crossed out or removed by molecular excision".

Furthermore the indication of “exogenous DNA deployed at any stage during the process” is unclear. E.g. oligonucleotides as used in ODM are small, synthesized molecules with no hereditary function. Indicating that exogenous DNA is necessary is in contradiction with the preceding text (line 263): “In case of ODM, the chemically synthetized oligonucleotide is directly delivered to the plant cell without the need of any stable or transient expression system.”

3.2.2.2.2 Alteration elsewhere in the genome [Section 4.2.2]

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Line 336/337: PlantEd suggests adding literature that contends that technology is evolving very quickly and the need to keep up and assess the emergence of the technology and its improvement on a regular basis to be able to appropriately address potential risks (see, e.g., Deng et al. 2019).

Line 347/349: PlantEd suggests referring to the report on “new techniques in agricultural biotechnology” prepared for the European Commission: https://ec.europa.eu/info/publications/new-techniques-agricultural-biotechnology_en.

Lines 340-358: PlantEd encourages EFSA to further elaborate on the fact that, just as for conventional mutagenesis (randomly induced in vivo and in vitro mutagenesis), subsequent generations of backcrossing will allow the removal of most potential off-target mutations. In any case, the number of off-target mutations will often be much less in the plants, and their derived products, developed using SDN-1, SDN-2 or ODM technology in comparison with those developed with conventional mutagenesis. In addition, it is important to note that these site-directed nuclease technologies are an integrated part of a larger breeding process, where off-types, unstable lines, and lines displaying unwanted phenotypes are regularly sorted out and eliminated.

Line 358: PlantEd suggests to include the conclusion on the same issue from the draft EFSA draft Scientific Opinion on Synthetic Biology developments in plants, molecular characterization (MC) and environmental risk assessment (ERA) aspects, because it has the same relevance for SDN-1, SDN-2 and ODM applications: “Therefore, taking into account all of the above, the GMO Panel considers that the analysis of potential off-targets on a regular basis would be of very limited value for the risk analysis.”

4. Conclusions

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The conclusions justify elaborating on proportionality and non-discrimination in view of similar and generally safe products resulting from conventional breeding practices as outlined at multiple instances above.

6. Reference

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EFSA (2012). Scientific opinion addressing the safety assessment of plants developed using Zinc Finger Nuclease 3 and other Site-Directed Nucleases with similar function. EFSA J. 10. doi:10.2903/j.efsa.2012.2943.
EFSA (2020). Applicability of the EFSA opinion on site-directed nucleases type for the safety assessment of plants developed using site-directed nucleases type and and oligonucleotide-directed mutagenesis. 16 pp. Available at: https://www.efsa.europa.eu/en/consultations/call/public-consultation-applicability-efsa-opinion-site-directed [Accessed May 5, 2020].
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DONG, C. , BEETHAM, P. , VINCENT, K. AND SHARP, P. (2006) Oligonucleotide-directed gene repair in wheat using a transient plasmid gene repair assay system. Plant Cell Rep. 25, 457–465.
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EU court casts new plant breeding techniques into regulatory limbo. Nat. Biotechnol. 36, 799–800. doi: 10.1038/nbt.4251.
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Sprink, T., Eriksson, D., Schiemann, J., and Hartung, F. (2016). Regulatory hurdles for genome editing: process- vs. product-based approaches in different regulatory contexts. Plant Cell Rep. 35, 1493–1506. doi: 10.1007/s00299-016-1990-2.
Vives-Vallés, J. A., and Collonnier, C. (2020). The Judgment of the CJEU of 25 July 2018 on Mutagenesis: Interpretation and Interim Legislative Proposal. Front. Plant Sci. 10, 1813. doi:10.3389/fpls.2019.01813.
Zhang, Y., Malzahn, A. A., Sretenovic, S., & Qi, Y. (2019). The emerging and uncultivated potential of CRISPR technology in plant science. Nature plants, 5(8), 778-794.

Other comments

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This opinion addresses specific sections of EFSA risk assessment guidance on molecular characterization and confirms convincingly that SDN-1, SDN-2 and ODM based directed mutagenesis is similar to and undistinguishable from mutations obtained by conventional breeding techniques, and that their application entail no new specific hazards. While acknowledging the suggested and scientifically justified reduction in molecular data requirements, there is no clarity on other data requirements.

PlantEd invites EFSA to present a clear problem formulation that spells out which of the requirements for risk assessment of GM plants, or food and feed products resulting from those plants, are essential in order to achieve a high level of safety for European consumers, animals and the environment. This level of safety should be comparable to the level for conventionally bred crops. This would help aligning the EU GMO risk assessment with the principle of proportionality.

Upload file(s) if necessary

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  - ◉ NO

Useful links

Guidance on the environmental risk assessment of genetically modified plants. EFSA Journal 2010 (https://www.efsa.europa.eu/en/efsajournal/pub/1879)

Guidance for risk assessment of food and feed from genetically modified plants. EFSA Journal 2011 (https://www efsa.europa.eu/en/efsajournal/pub/2150)

Privacy_Notice (https://www.efsa.europa.eu/sites/default/files/consultation/consultation/Privacy_notice_EFSA_PC2020.pdf)

Editorial "Advances in genetic engineering" (https://efsa.onlinelibrary.wiley.com/doi/10.2903/j.efsa.2020.e18021)

Background Documents

Opinion_on_SDN3_EFSA_Journal_2012.pdf

Scientific_opinion_SDN1_2_ODM.pdf

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