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Criteria for risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis

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Abstract

EFSA was asked by the European Commission to develop criteria as advice for consideration for the risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis. EFSA proposes in this statement six main criteria to assist the risk assessment of these plants. The first four criteria are related to the molecular characterisation of the genetic modification introduced in the recipient plant. The four criteria evaluate whether any exogenous DNA sequence(s) is/are present (Criterion 1), whether such sequence derives from the breeders' gene pool (Criterion 2), the type of integration (Criterion 3) and whether any endogenous plant gene is interrupted (Criterion 4). Depending on the evaluation of the above criteria, the product can be a genome edited plant where no exogenous DNA sequence is present, or a cisgenic or intragenic plant where the cisgenic and intragenic sequence are introduced by targeted insertion and no plant endogenous genes are interrupted. In these cases, two more criteria are assessed to evaluate the history of safe use (Criterion 5) and the structure and function of the new allele (Criterion 6). If cisgenic and intragenic sequence are introduced by random integration without interruption of an endogenous gene, or when no risk is identified when an endogenous gene is interrupted, the criteria 5 and 6 will also be assessed. Evaluating the history of safe use is an important part of the proportionate risk assessment of cisgenic, intragenic and genome-edited plants since the newly introduced allele may already be present in nature. However, when the history of safe use cannot be sufficiently demonstrated, the function and structure of the introduced allele should be carefully assessed. Recommendations are also included on the aspects that need further elaboration for full applicability of the criteria proposed herein are also included.

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1. Introduction

On 28 April 2022, the European Commission requested the European Food Safety Authority (EFSA), in accordance with Article 31 of Regulation (EC) No 178/2002, to develop an EFSA statement on possible criteria for risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis (Ref. Ares(2022)3302985).¹ The statement was requested as an advice for consideration by the European Commission to support the ongoing policy initiative on plants produced by targeted mutagenesis and cisgenesis.²

1.1. Background³

The Commission is conducting an impact assessment with a view to a possible legal proposal on plants and their food and feed products produced by targeted mutagenesis, cisgenesis and intragenesis based on the outcome of a study on new genomic techniques (NGTs)⁴ requested from the Commission by the Council⁵ and published on 29 April 2021.

Among NGTs, some of the modifications of the genetic material obtained by targeted mutagenesis, cisgenesis or intragenesis could also be obtained by natural mutations/variations and conventional breeding techniques. The above-mentioned EC study took into account available scientific opinions of the European Food Safety Authority (EFSA)⁶ and concluded that current regulatory oversight and requirements are not adapted to the diverse risk profiles of plants produced by targeted mutagenesis, cisgenesis and intragenesis, and in some cases can be disproportionate or inadequate.

In particular, EFSA considered that plants produced by targeted mutagenesis, cisgenesis and intragenesis, in some cases, do not pose new hazards compared to plants produced with classical mutagenesis or conventional breeding techniques. For plants produced by targeted mutagenesis, EFSA concluded that the amount of experimental data needed for the risk assessment mainly depends on the modified trait introduced and, on a case-by-case basis, less experimental data would be needed compared to plants produced by transgenesis, intragenesis or cisgenesis.⁶ As for cisgenesis and intragenesis, EFSA concluded that it can be envisaged that on a case-by-case basis less event-specific data are needed for the risk assessment of these plants compared to transgenic plants.⁶

Based on this and aiming at an appropriate regulatory oversight that maintains a high level of protection of human and animal health and of the environment, the Commission has identified a number of policy elements to be considered in the proposed initiative. These include risk assessment and approval requirements proportionate to the risk involved, e.g. in terms of data and studies, in line with risk profiles and on a case-by-case basis, taking into account criteria such as the specific technique used, the type of modification or the novelty of the trait.⁷ Such a list of criteria needs to be further developed and could be used to support the evaluation, on a case-by-case basis, of the type and amount of data required to perform the risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis.

1.2. Terms of Reference⁸

Against the above background and building on previous work of EFSA on the matter, the European Commission asks EFSA, in accordance with Article 31 of Regulation (EC) No 178/2002, to provide a statement, as advice for consideration by the European Commission, on possible criteria for the risk

¹ <https://open.efsa.europa.eu/questions/EFSA-Q-2022-00309>

² https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques_en

³ In the Commission's policy initiative, cisgenesis is defined as the insertion of genetic material (e.g. a gene) into a recipient organism from a donor organism with which the recipient is sexually compatible (crossable) in nature. The Commission definition encompasses cisgenesis and intragenesis as defined in the EFSA GMO panel Scientific opinion on cisgenesis and intragenesis. For consistency and clarity between the mandate, the EFSA opinions and its conclusions, this EFSA statement will refer to both cisgenesis and intragenesis. For this reason, the text provided by European Commission reported in this section was adapted to include intragenesis.

⁴ https://food.ec.europa.eu/plants/genetically-modified-organisms/new-techniques-biotechnology/ec-study-new-genomic-techniques_en

⁵ <https://eur-lex.europa.eu/eli/dec/2019/1904/oj>

⁶ <https://www.efsa.europa.eu/en/efsajournal/pub/2561>, <https://www.efsa.europa.eu/en/efsajournal/pub/2943>, <https://www.efsa.europa.eu/en/efsajournal/pub/6299>

⁷ See inception impact assessment of the initiative at https://ec.europa.eu/info/law/better-regulation/have-your-say/initiatives/13119-Legislation-for-plants-produced-by-certain-new-genomic-techniques_en

⁸ Text provided by European Commission was adapted to also include intragenesis.

assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis. The term “criteria” under the present mandate should be understood as referring to elements (e.g. the specific technique used, the type of modification or the novelty of the trait) that should be taken into account to evaluate, on a case-by-case basis, the type and amount of data required to perform the risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis. Under the present mandate, EFSA is not requested to develop actual data requirements for the risk assessment of these plants.

2. Data and methodologies

2.1. Data

To develop this statement, EFSA took into consideration previous published EFSA Opinions on targeted mutagenesis, cisgenesis and intragenesis as indicated in Section 1.1 (EFSA GMO Panel, 2012a,b, 2020, 2022a). EFSA also considered those assessment aspects discussed by the GMO Panel in the EFSA Opinions on plants developed through synthetic biology approach (EFSA GMO Panel, 2021, 2022b) which are relevant for the risk assessment of plants developed through targeted mutagenesis, cisgenesis and intragenesis.

2.2. Methodologies

The European Commission requested EFSA to address this mandate by taking into consideration the assessment and conclusions already published in previous EFSA Scientific Opinions (Section 2.1). This statement includes data that have already been assessed and discussed in previous EFSA Scientific Opinions. Therefore, a protocol to plan the scientific assessment method was deemed unnecessary for this mandate.

2.3. Definitions

The following definitions apply to this statement:

- **Breeders’ gene pool:** the sources of genes/alleles available for conventional plant breeding are referred to as the ‘breeders’ gene pool’. Breeders distinguish between primary, secondary and tertiary gene pools. Each primary gene pool comprises one cultivated species and other taxonomic species with which it can interbreed freely. The secondary gene pool includes species that can be cross-bred only with difficulty with a member of the primary gene pool but which produce at least some fertile hybrids. The tertiary gene pool comprises those species that are more distantly related to a member of the primary gene pool but which can be cross-bred only using advanced techniques such as embryo rescue, induced polyploidy and bridge crosses. Breeders are continually expanding the tertiary gene pool and will continue to do so in the future (EFSA GMO Panel, 2012a, 2022a).
- **Cisgenesis:** a genetic modification involving genetic material obtained from the breeders’ gene pool and transferred to the host using various delivery strategies; the incorporated sequences contain **an exact copy** of a sequence already present in the breeders’ gene pool (adapted from the terms of reference of the EFSA mandate ‘Request for an updated scientific opinion on plants developed through cisgenesis and intragenesis’)⁹ (EFSA GMO Panel, 2022a).
- **Established genetic techniques:** abbreviated to EGTs, genomic techniques developed before 2001, when the Directive 2001/18/EC¹⁰ was adopted.
- **Exogenous DNA sequence:** DNA produced by whatever means outside of the target organism (Annex IA Part 1 of Directive 2001/18/EC¹⁰).
- **Intragenesis:** a genetic modification involving genetic material obtained from the breeders’ gene pool and transferred to the host using various delivery strategies; the incorporated sequences contain **a re-arranged copy** of sequences already present in the breeders’ gene pool (adapted from the terms of reference of the EFSA mandate ‘Request for an updated scientific opinion on plants developed through cisgenesis and intragenesis’)¹¹ (EFSA GMO Panel, 2022a).

⁹ Adapted from <https://open.efsa.europa.eu/study-inventory/EFSA-Q-2021-00361>

¹⁰ Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC.

¹¹ Available at <https://open.efsa.europa.eu/study-inventory/EFSA-Q-2021-00361>

- **Oligonucleotide:** A stretch of nucleic acid consisting of a relatively low number of nucleotides (EFSA GMO Panel, 2020).
- **Oligonucleotide-directed mutagenesis:** abbreviated to **ODM**, an approach which is based on the use of oligonucleotides for the introduction of targeted mutations in the genome, usually of one or a few adjacent nucleotides. The genetic changes that can be obtained using ODM include substitutions, insertions or deletions (EFSA GMO Panel, 2020).
- **Site directed nuclease:** abbreviated to **SDN**, an enzyme that recognises a specific sequence and cleaves the DNA usually creating a double-strand break (EFSA GMO Panel, 2020). Three types of SDN approaches can be used:
 - **SDN-1:** site-directed nuclease type 1 introduces random mutations (substitutions, insertions, and deletions) at the target plant genomic site (EFSA GMO Panel, 2020).
 - **SDN-2:** site-directed nuclease type 2 makes use of template DNA to generate a predicted modification (i.e. intended sequence modification) at the target plant genomic site (EFSA GMO Panel, 2020).
 - **SDN-3:** site-directed nuclease type 3 introduces large stretch of donor DNA (up to several kilobases) into a predefined genomic locus (EFSA GMO Panel, 2012b).
- **Transgenesis:** the process of stably introducing gene(s) from any sexually incompatible species, or any synthetic gene non existing in nature, into the genome of a given cell and the propagation of such gene(s) thereafter (EFSA GMO Panel, 2020).
- **Targeted mutagenesis:** an umbrella term used to describe newer techniques of mutagenesis that induce mutation(s) in selected target locations of the genome.¹² For the purpose of the mandate, SDN-3 approaches are not included when they introduce sequence(s) from outside the breeders' gene pool.

The following terms used in this statement are derived from the above definitions:

- **Cisgenic plant:** a plant obtained by cisgenesis [e.g. via EGTs or SDN-3]
- **Intragenic plant:** a plant obtained by intragenesis [e.g. via EGTs or SDN-3]
- **Transgenic plant:** a plant obtained by transgenesis
- **Genome edited plant:** abbreviated to **GE plant**, a plant obtained by the application of targeted mutagenesis techniques

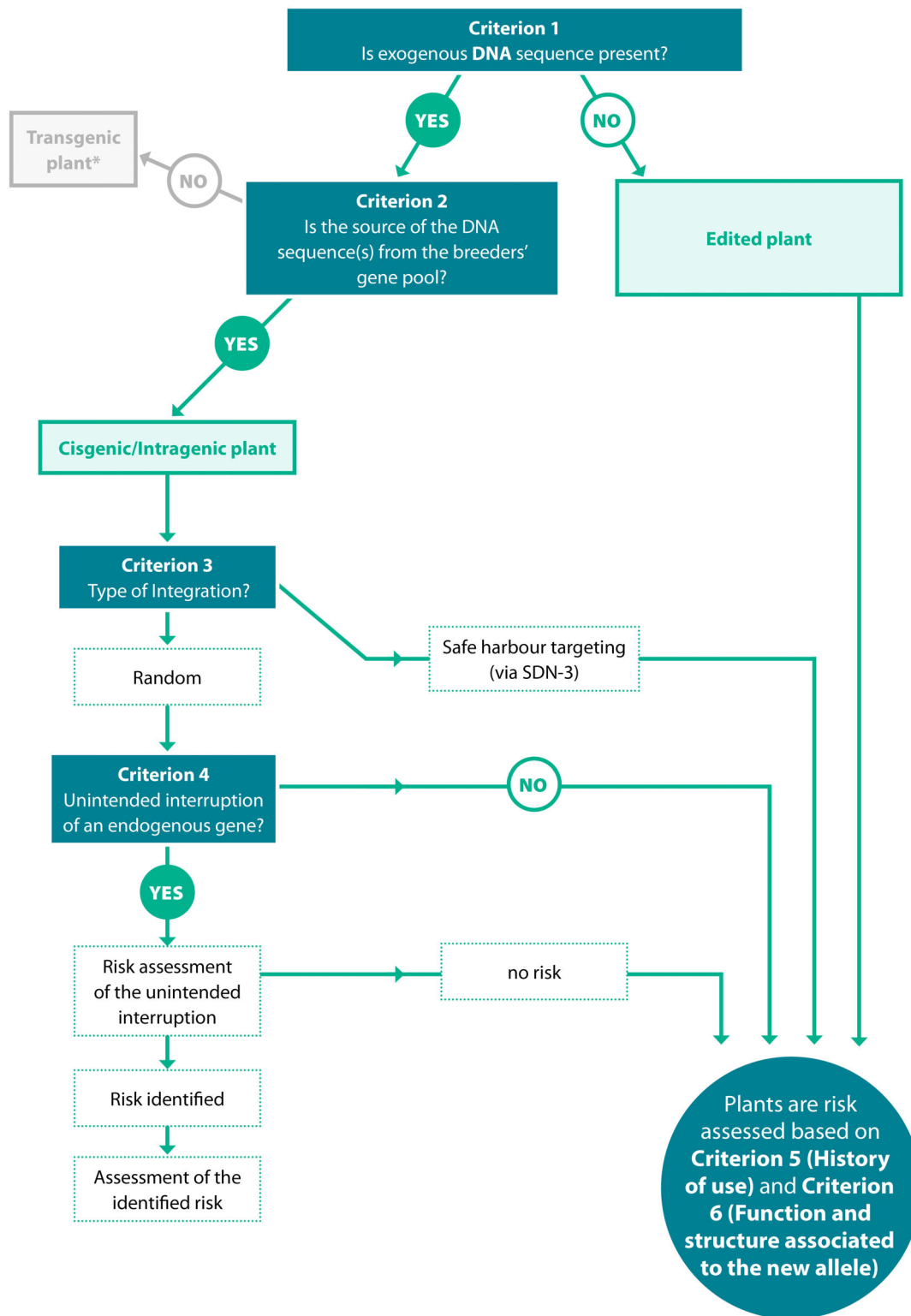
3. Criteria for risk assessment of plants and their products developed through targeted mutagenesis, cisgenesis and intragenesis

The proposed criteria described in the sections below are considered as 'elements that should be taken into account to evaluate, on a case-by-case basis, the type and amount of data required to perform the risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis', as per the terms of reference.

The proposed criteria were developed taking into consideration (i) the molecular characteristics of the genetic modification(s) introduced into a GM plant and (ii) the characteristics of the expressed trait regarding the food and feed (FF) and the environmental risk assessment (ERA) aspects.

A decision tree summarising the criteria is proposed in Figure 1. The rationale for the proposed criteria is described in the following sections.

¹² Adapted from the European Commission study on new genomic techniques. Available at: https://ec.europa.eu/food/system/files/2021-04/gmo_mod-bio_ngt_eu-study.pdf (Annex A).



*Please note that plants obtained by transgenesis are out of the scope of the EC initiative to propose a legal framework for plants obtained by targeted mutagenesis and cisgenesis and for their food and feed products.

Figure 1: Decision tree according to proposed EFSA criteria for the risk assessment of plants developed through targeted mutagenesis, cisgenesis and intragenesis

3.1. Criterion 1: is any exogenous DNA sequence(s) present?

The first criterion is based on the molecular characterisation of the genetic modification introduced in the genome of the GM plant. Specifically, **Criterion 1** aims to evaluate whether the GM plant contains any exogenous DNA sequence (see definition in Section 2.3). Two possible scenarios can be distinguished:

- 1) **The GM plant contains exogenous DNA sequence(s):** in this case, the source of the DNA sequence must be considered according to criteria 2, 3 and 4 (proceed to **Section 3.2**).
- 2) **The GM plant does not contain any exogenous DNA sequence(s):** the GM plant has been created by targeted mutagenesis, for example, using SDN-1 or SDN-2 approaches, generating a GE plant. The GE plant is free from any exogenous DNA sequence (EFSA GMO Panel, 2020) and hence risk assessment approach should proceed according to **Section 3.5**.

3.2. Criterion 2: is the DNA sequence(s) from the breeders' gene pool?

The GM plant which contains exogenous DNA sequence(s) will be evaluated under **Criterion 2**, which assesses whether the source of the DNA sequence(s) is from the breeders' gene pool (see definition in Section 2.3; EFSA GMO Panel, 2012a). Two possible scenarios can be distinguished under Criterion 2:

- 1) **The DNA sequence(s) is not from the breeders' gene pool:** the GM plant, which contains any exogenous DNA sequence(s) outside the breeders' gene pool, is considered a transgenic plant. The risk assessment is performed according to the requirements currently implemented for the risk assessment of GM plants.¹³ It should be noted that transgenic plants are out of the scope of the EC initiative and this mandate, as described in Section 1.1. Therefore, they are not further discussed in this statement.
- 2) **The DNA sequence(s) is from the breeders' gene pool:** the GM plant has been generated via cisgenesis or intragenesis approaches generating a cisgenic or intragenic plant according to the definitions provided in Section 2.3 and the EFSA Scientific Opinions (EFSA GMO Panel, 2012a, 2022a). Therefore, the risk assessment approach should proceed according to Criterion 3 (proceed to **Section 3.3**).

3.3. Criterion 3: what is the type of integration?

Criterion 3 applies only to cisgenic and intragenic plants (Section 3.2, point 2). The cisgenic and intragenic sequence can be introduced through:

- 1) EGTs that would *randomly* introduce a cisgenic and intragenic sequence in the plant genome (EFSA GMO Panel, 2012a, 2022a). The obtained cisgenic or intragenic plant can be further categorised based on Criterion 4 (proceed to **Section 3.4**).
- 2) SDN-3 that would insert the cisgenic and intragenic sequence in a genomic locus which is decided *a priori* (EFSA GMO Panel, 2012a,b, 2022a). For plants produced using a successful SDN-3 strategy, there will be cases where the potential for unintended effects (e.g. positional and off-target effects) is significantly reduced compared to random insertions or conventional breeding (EFSA GMO Panel, 2012b, 2022a). Therefore, there is a need for flexibility in the data requirements for risk assessments of GM plants produced by proven Genomic Safe Harbors (GSH) SDN-3 approaches (EFSA GMO Panel, 2012a,b, 2022a). Therefore, the risk assessment approach should proceed according to **Section 3.5**.

¹³ Directive 2001/18/EC of the European Parliament and of the Council of 12 March 2001 on the deliberate release into the environment of genetically modified organisms and repealing Council Directive 90/220/EEC. OJ L 106, 12.3.2001, p. 1–38. Regulation (EC) No 1829/2003 of the European Parliament and of the Council of 22 September 2003 on genetically modified food and feed. OJ L 268, 18.10.2003, p. 1–23. Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. OJ L157, 8.6.2013, p. 1–48. Applicable EFSA guidance <https://www.efsa.europa.eu/en/applications/gmo/regulationsandguidance>

3.4. Criterion 4: is there an unintended interruption of an endogenous gene?

Criterion 4 applies only to cisgenic or intragenic plants for which the type of insertion was random (Section 3.3, point 1) or for SDN-3 approaches for which GSH has not been demonstrated. The assessment of the effect of the insertion may lead to two possible scenarios:

- 1) in case (i) an endogenous plant gene has been disrupted but following the risk assessment, no risk is identified, or (ii) no endogenous genes have been disrupted at all, the risk assessment approach should proceed according to **Section 3.5**.
- 2) in case an endogenous gene has been disrupted and following the risk assessment, a risk is identified, the assessment of such risk shall be performed.

3.5. Criterion 5: history of use

The history of use includes the history of safe use (HoSU) for consumers and/or animals and familiarity for the environment which are key elements in the assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis. Considerations on the HoSU and familiarity may assist in determining the type and amount of data required to perform the risk assessment of these plants.

The HoSU concept for consumers and/or animals has been utilised by the GMO panel in consideration of GM plants produced by targeted mutagenesis, cisgenesis and intragenesis (EFSA GMO Panel, 2012a, 2020, 2021, 2022a) and by other EFSA panels (e.g. EFSA, 2009; EFSA ANS Panel, 2012; Regulation (EU) 2015/2283 on novel food¹⁴). Demonstration of a HoSU is based on evidence that some or all of a plant has been consumed in the diet (food and/or feed and derived products) for a considerable time with no evidence of adverse effects being produced, and that exposures from a new use will be within the range of those from the 'historic' use. For example, Canada estimates HoSU for Novel foods based on the number of generations that consumed such products, while Europe refers to a time frame of at least 25 years of consumption (Fernandez and Paoletti, 2018). The concept of familiarity for the environment is enshrined in the EFSA guidance for the environmental risk assessment of GMOs (EFSA GMO Panel, 2010) and has been discussed in previous EFSA Opinion in relation to SDN-3, cisgenesis and intragenesis (EFSA GMO Panel, 2012a,b).

In addition, some aspects of HoSU for consumers and/or animals that should be considered could be:

- Whether the introduced or modified gene and its product in the native species are already consumed as a significant part of the diet or only consumed occasionally at low levels. Is the new consumption pattern altered compared to that of the past use? Which parts or tissues of the currently consumed plant are in the diet? Does this adequately cover the new use?
- Whether any specific processing steps are required before the currently consumed plant is consumed safely (e.g. soaking, prolonged cooking, removal of certain parts). Will these steps need to be applied to the new use and is this feasible?
- Whether the intake of nutrients, vitamins, allergens and toxins from the new use is within those of the historic use or within acceptable levels based on the general diet. Paying attention to any parts of the new organism which might have particularly high or low levels of some components.

Regarding Criterion 5, two possible scenarios can be distinguished following the history of use assessment:

- A) **HoSU and/or familiarity can be demonstrated:** the donor plant and/or the gene/allele and the associated trait has a history of consumption as food and feed and/or familiarity for the environment (EFSA GMO Panel, 2012a). For example, the DNA sequence obtained through targeted mutagenesis, cisgenesis or intragenesis and the associated trait are already present in a consumed variety. In other cases, the donor plant may not have a history of consumption as food and feed, but it may have been used in conventional breeding to introgress alleles conferring agronomically important traits. In this case, the risk assessment may focus on the knowledge of that bred variety, the specific modified or introduced allele

¹⁴ Regulation (EU) 2015/2283 of the European Parliament and of the Council of 25 November 2015 on novel foods, amending Regulation (EU) No 1169/2011 of the European Parliament and of the Council and repealing Regulation (EC) No 258/97 of the European Parliament and of the Council and Commission Regulation (EC) No 1852/2001.

and the intended trait (i.e. HoSU). When the HoSU can be demonstrated, certain data on the edited sequence(s), the cisgenic and intragenic sequence and their product(s) may not be needed for the risk assessment. Moreover, the familiarity for the environment may help to reduce the level of scientific uncertainty associated with the novel plant and hence the number of hypotheses to be tested in the risk characterisation phase (EFSA GMO Panel, 2012a, 2020). Several examples for which the HoSU can be demonstrated were discussed by the GMO Panel in the previous EFSA Opinion [see Section 4.1 in EFSA GMO Panel (2012a)].

- B) **HoSU and/or familiarity cannot be demonstrated:** The gene/allele and associated trait has not been shown to be present in a plant having a history of consumption as food and feed and/or cultivation (EFSA GMO Panel, 2012a). In this case, the risk assessment may focus on the function and structure associated to this allele and hence risk assessment should proceed according to **Section 3.6**.

3.6. Criterion 6: function and structure associated to the new allele

When the HoSU and/or familiarity cannot be sufficiently demonstrated, the risk assessment should focus on the function and the structure associated to the new allele. The risk assessment should also consider the probability for such an allele to be obtained by conventional breeding (natural or induced variation). In case the newly introduced allele is from a crossable species, but the familiarity cannot be demonstrated, the fact that this allele is in the breeders' gene pool should be taken into consideration when assessing the safety of the gene product.

Additional aspects of the newly introduced or modified allele should be taken into consideration for the risk assessment, for example:

- Whether the initial function of the modified allele is conserved or whether the new allele gained any additional function compared to the original one.
- Whether the new allele has the potential to generate a product that may be toxic or allergenic.
- Whether the new allele is characterised by an altered expression level compared to the native one or whether the allele's product displays a different localisation/compartimentalisation compared to the native one.

The aspects described above may help in guiding the risk assessment. However, it should be noted that an exhaustive list cannot be provided in this statement considering the vast array of products that can be generated by targeted mutagenesis, cisgenesis and intragenesis.

4. Additional considerations

To develop these criteria, EFSA used the information already elaborated and discussed in relevant published EFSA Scientific Opinions (EFSA GMO Panel, 2012a,b, 2020, 2021, 2022b). In those Opinions, EFSA highlighted certain aspects that require further discussion, particularly relevant for complex products, and their safety evaluation according to the current regulatory framework and applicable EFSA guidances.¹³ In some of these cases, multiple genetic modifications can be introduced simultaneously in the plant, using targeted mutagenesis approaches. These mutations may not be genetically linked, similarly to transgenic GM plants with stacked events. EFSA concluded that the assessment of the single modification first, similarly to what is currently required by the Implementing Regulation (EU) 503/2013¹⁵, may be challenging or even unfeasible for plants with a high number of inserted/modified sequences [see Case Study 2 'Non-transgenic, gluten-free wheat' in EFSA GMO Panel (2021)]. Furthermore, in case multiple plant endogenous genes are modified by targeted mutagenesis to produce many novel proteins, EFSA concluded that the assessment all these new proteins would also be challenging according to the current regulatory framework (EFSA GMO Panel, 2022b,c). EFSA concluded that the comparative analysis may not always be applicable to some genome-edited plants with complex traits for which a comparator cannot be identified (EFSA GMO Panel, 2021, 2022b). In this case, the current guidelines, although adequate, should be revised to support the risk assessment of these plants by either using the comparative analysis against multiple comparators or by a stand-alone assessment for which an appropriate procedure should be developed

¹⁵ Commission Implementing Regulation (EU) No 503/2013 of 3 April 2013 on applications for authorisation of genetically modified food and feed in accordance with Regulation (EC) No 1829/2003 of the European Parliament and of the Council and amending Commission Regulations (EC) No 641/2004 and (EC) No 1981/2006. OJ L157, 8.6.2013, p. 1–48., Annex II, Section 2.

[see Case Study 4 in EFSA GMO Panel (2022b)]. Finally, EFSA refers to the consideration already included in previous Opinions regarding the analysis of the potential off-targets induced by the application of targeted mutagenesis techniques (EFSA GMO Panel, 2012b, 2020).

5. Conclusions and recommendations

Upon request from the European Commission, EFSA proposed in this statement several criteria for the risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis. The criteria proposed should be regarded as advice for consideration by the European Commission.

The current risk assessment approach aims at identifying potential unintended effects by the molecular characterisation and the comparative assessment steps (EFSA GMO Panel, 2022b). However, taking into consideration the criteria proposed in this document and given the challenges discussed in Section 4, the identification of the unintended effects should rely on the HoSU/familiarity and/or on the investigation of the function and structure associated with the modified (in case of genome-edited plants) or inserted (in case of cisgenic and intragenic plants) sequence/allele.

Finally, the HoSU is a key point in the proportionate risk assessment. Some general considerations on HoSU, although not exhaustive, are given in this statement. EFSA recommends that a definition of HoSU is developed in the near future to support the risk assessment in the context of this statement and other areas where the concept is utilised.

The aspects of the risk assessment described above should be considered as recommendations that should be further elaborated to allow the full applicability of the criteria described in this statement and do not indicate data requirements for the risk assessment of these plants.

6. Documentation as provided to EFSA

- Mandate from the European Commission (EC) received on 28 April 2022 concerning a request for an "EFSA statement on the criteria for risk assessment for plants produced by targeted mutagenesis and cisgenesis".
- Mandate accepted on 10 May 2022.
- Letter from the European Commission (EC) to EFSA on 25 August 2022 requesting an update of the original request.

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Abbreviations

EGT	established genomic technique
GE	genome edited
GM	genetically modified
GSH	genomic safe harbours
HoSU	history of safe use
NGT	new genomic technique
ODM	oligonucleotide directed mutagenesis
SDN	site directed nuclease