



ESTABLISHMENT, TERMS OF REFERENCE (TOR) AND OBJECTIVES OF THE SUBGROUP ON NGTS

1st Subgroup on NGTs – Brussels – 29th May 2024

CONTENT

WHY and HOW:

1. 89th Advisory Forum meeting (October 2023)
2. 90th Advisory Forum meeting (November – December 2023)
3. GMO Network meeting (December 2023)
4. 91st Advisory Forum meeting (March 2024)
5. Establishment and first meeting of the Subgroup on NGTs



ADVISORY FORUM

Representatives from 27 Member States, Iceland and Norway + Switzerland, 7 Pre-Accession countries and EC, as Observers

Programming and prioritisation of EFSA & MS work, preventing duplication of effort

Scientific cooperation, sharing of information and best practices, making best use of resources

Coherence, avoiding divergent views

Identification of emerging risks



BACKGROUND (1)

89th Advisory Forum meeting (4-5 October 2023, 7.2. EFSA highlights on NGT) [LINK](#):

- EFSA presented an overview of the relevant discussions on NGTs that took place at the GMO Network meetings in the last three years
- **In April 2022**, the network reflected on proportionate RA and case-by-case approach and discussed **the possible criteria for proportionate risk assessment of NGT plants**
- **In November 2022**, following the **EFSA presentation of two documents**, namely **the criteria for RA of NGT plants and the updated opinion on cisgenesis and intragenesis**, the network discussed the criteria proposed by EFSA within those documents



BACKGROUND (2)

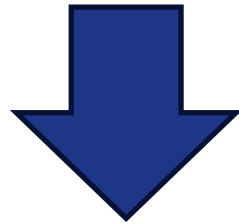
90th Advisory Forum meeting (30 November 2023 – 1 December 2023 - 7.3.d) Update about collaboration on New Genomic Techniques Risk Assessment) [LINK](#):

- Risk assessment of plants developed using **new genomic techniques presents challenges**
- Knowledge sharing with Member states is fundamental. The proposal to create a **focus group** involving **MS experts** will be discussed at the next meeting of the GMO MS scientific network (i.e. 13 Dec 2023)
- The goal is to achieve **wide engagement and acceptance of future RA guidance and address challenges consciously**, ensuring effective communication and understanding among Member States throughout the process.
- **Action 6** (EFSA/MS Item 7.3.d) - EFSA and MS to discuss MS collaboration and contribution to future guidance development.



BACKGROUND (3)

- **In December 2023**
 - both the AF and the GMO network of Member States welcomed EFSA's proposal to set up a sub-group of the GMO network on NGTs to foster knowledge sharing and jointly address the risk assessment challenges



Decision taken to establish a *'Subgroup on NGTs'*



PROCESS OF ESTABLISHING THE SUBGROUP ON NGTs (1)

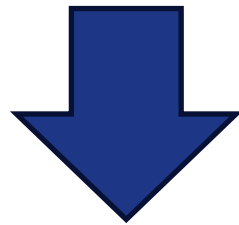
1. EFSA to draft Terms of Reference (modification of the existing GMO Net ToRs)
2. Advisory Forum to comment ToRs (1 month)
3. EFSA revises the ToRs and addresses the comments
4. ToR endorsed by the Advisory Forum
5. Advisory Forum nominates the participants and alternates according to the specifications in ToRs (1 month)



PROCESS OF ESTABLISHING THE SUBGROUP ON NGTs (2)

91st Advisory Forum meeting (6-7 March 2024 - 10.1.b) New Sub-group on “New Genomic Techniques” of the Scientific Network on Risk Assessment of Genetically Modified Organisms) [LINK](#):

- HoD described the creation of a subgroup **within** the GMO Network dedicated to new genomic techniques (NGTs)
- The need to amend the terms of reference and nominate representatives for the subgroup [...] To expedite the process, the speaker proposed concurrent endorsement of the modifications and nominations
- **EFSA clarified that the subgroup will serve as a consultative body for EFSA’s Working Groups and Panel**



Advisory Forum agreed to do Step 2 and Step 5 in 4 weeks to allow the organization of the 1st meeting on 29th May 2024



TERMS OF REFERENCE (LAST UPDATED: 7 MAY 2024)

- According to Art. 6.1 of the *Decision concerning the establishment and operation of European Networks of scientific organisations operating in the fields within the Authority's mission*,

...following the receipt of all necessary information from EFSA...

the **Advisory Forum** shall identify organisations in EU Member States which are capable of contributing to the tasks of the GMO Network.

The **Advisory Forum**, in cooperation with the member organisations formally designated in accordance with the previous paragraph, **shall establish the names of network participants and alternate participants** for the GMO Network within the designated member organisation(s)



TERMS OF REFERENCE

- The members of the **Subgroup on NGTs** should have professional and scientific background in the field of NGTs (e.g., molecular biology and genetics, genomic techniques, bioinformatic) and **experience in the area of molecular characterization (MC), food and feed (FF), and/or environmental risk assessment (ERA)** of GMOs, including plants, animals and microorganisms.
- Member States interested in joining the Subgroup on NGTs may appoint **one participant and one alternate**
- The Advisory Forum in collaboration with the national Focal Points members may liaise with the nominated members of the EFSA GMO Network to identify the candidates fulfilling the criteria
- The content and the outcome of any discussions within the Subgroup on NGTs are reported back to the GMO Network for possible further elaboration



TERMS OF REFERENCE

Main Objective of the Subgroup on NGTs:

- The main objective of the Subgroup on NGTs is **to foster knowledge sharing** on the development of NGTs, their application to plants, animals and microorganisms **and jointly address the risk assessment and monitoring challenges** specifically linked to NGTs applied to plants, animals and microorganisms.

...And from the 91st AF meeting:

- **the subgroup will serve as a consultative body for EFSA's Working Groups and Panel**



WORKING MODALITIES

Meetings:

- The network shall meet physically or virtually at least once per year.
- The working language for the Network activities will be English.
- The Subgroup on NGTs will meet according to the identified needs, ensuring ample advance notice to allow proper meeting arrangements.
- In-person and on-line meetings (same procedure as for the GMO Network)
- Teams channel available (do you have access?)

Outcomes:

- The proceedings of GMO Network **and the subgroup on NGTs** meetings shall be recorded in meeting minutes. After adoption, these minutes will be published on the EFSA website.
- The activities of the GMO Network and the subgroup on NGTs, as well as the examination of the criticalities found, shall be recorded **in annual technical reports issued by EFSA**. These reports will be published on the EFSA website and presented to the EFSA Advisory Forum.



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INTRODUCTION OF THE CASE STUDIES AND DISCUSSION ON THE RA METHODOLOGIES FOR PLANTS OBTAINED VIA NGTS



GMO Network
Subgroup on NGTs
1st Meeting 29 May 2024 - Brussels

ACTIVITIES

- Objectives of the meeting
 - Presentation of the case studies on plants obtained via NGTs
 - Discussion on risk assessment approaches (group discussion)
 - Criteria for risk assessment of plants produced by targeted mutagenesis, cisgenesis and intragenesis
 - Identification on areas which need further discussion and/or development

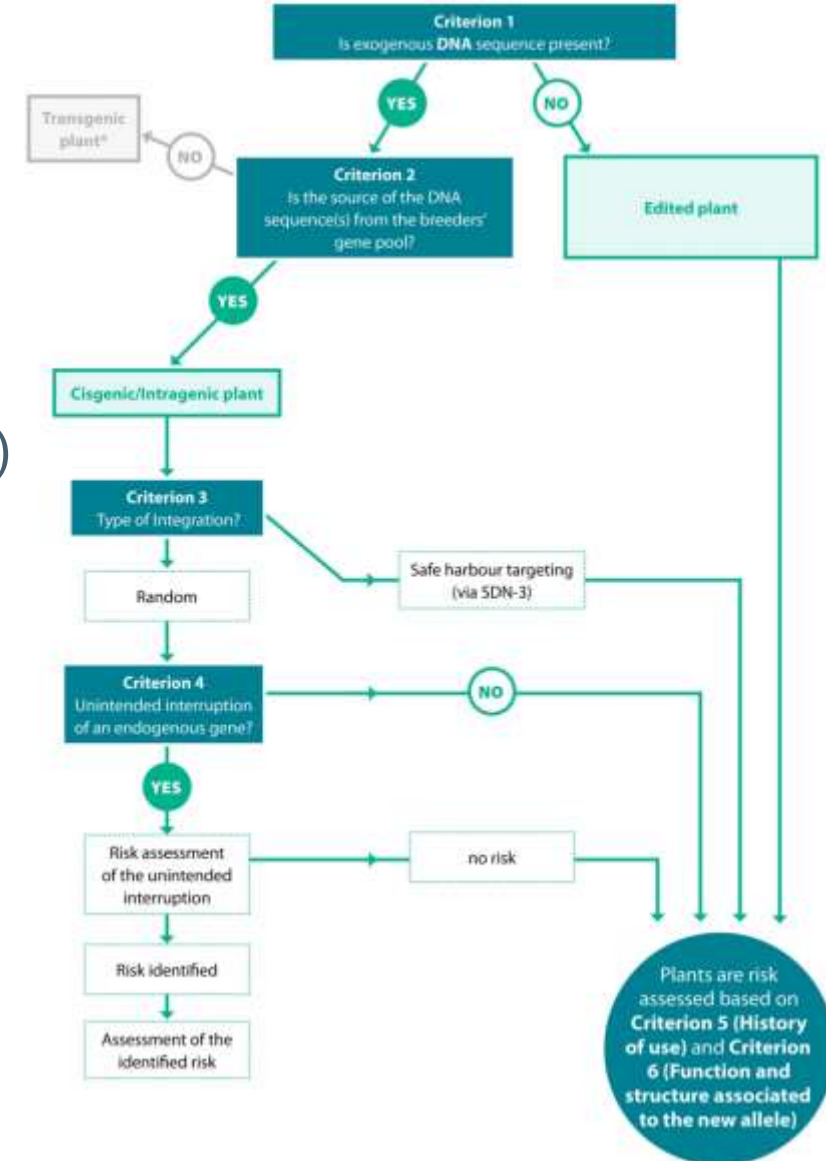


SUMMARY OF PREVIOUS MAIN CONCLUSIONS OF THE EFSA CRITERIA FOR RA OF NGT PLANTS

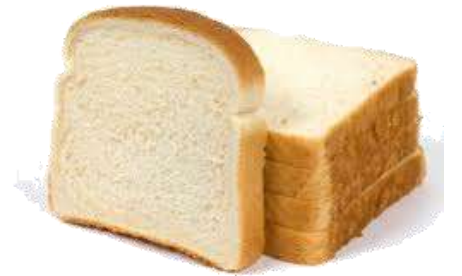
INVOLVEMENT ?		
MC	Comp ERA	FF
YES	-	-
YES	-	-
YES	-	-
YES	YES	-
YES	YES	YES
YES	YES	YES

CRITERIA

1. **Exogenous DNA**
2. Source of the new (**breeders' gene pool**)
3. Integration (**random/targeted**)
4. **Gene interruption**
5. History of safe use (**HoSU**)?
6. **Function and structure**



Case study 1 ([Sánchez-León S, et al., 2018](#))



Crop: common wheat

Intended trait: reduced α -gliadin content

Technique: CRISPR/Cas9 construct targeting >30 *Gli-2* loci. The CRISPR/Cas9 produced indels at the target loci obtaining a knock-down of the α -gliadin.

The CRISPR/Cas9 cassette will not be present in the final wheat.

Case study 2 (hypothetical)

Crop: durum wheat

Intended trait: leaf rust (Lr) resistance

Technique: 10 CRISPR/Cas9 targeting 10 endogenous *Lr* gene. The endogenous genes will be replaced with *Lr* genes from a wild relative conferring broader resistance. In addition, 15 endogenous 'susceptibility genes' were disrupted via CRISPR/Cas9 approach to promote a durable resistant phenotype.

The CRISPR/Cas9 cassette will not be present in the final wheat.





Current requirements for GMOs per RA area (brief overview)



THE 4 PILLARS OF THE CURRENT GMO RA

1
Molecular
characterisation
(MC)



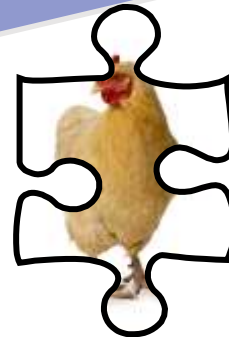
- Description of methods,
- Info on vectors, inserted/deleted sequence(s), new traits
- Info on the protein expression levels, protein characterization
- Bioinformatics data
- Genetic and phenotypic stability

2
Comparative
analysis (CA)



- Agronomic and phenotypic characteristics,
- Compositional data

3
Food/Feed risk
assessment (FF)



- Toxicological assessment
- Allergenicity assessment
- Dietary exposure
- Nutritional assessment
- PMM

4
Environmental
risk assessment
(ERA)



- Persistence/invasiveness
- Gene flow
- (non-)target organisms
- Abiotic environment
- PMEM



REQUIREMENTS MC

Molecular characterisation

1. Description of the methods used for the genetic modification
2. Nature and source of the vector used
3. Information on the donor organism(s)
4. Information on the nucleic acid(s) sequence(s) intended to be inserted
5. Description of the introduced trait(s), of the resulting changes on phenotype and metabolism of the GM plant
6. Information on the sequences actually inserted/deleted: Sequencing package/report
7. Copy number and size of all detectable inserts
8. Flanking sequences
9. Open reading frames in flanks
 1. similarity to known allergens
 2. similarity to known toxins
10. Open reading frames in the insert
 1. similarity to known allergens
 2. similarity to known toxins
11. Protein expression study
12. NEPs
 1. sequence similarities to known allergens
 2. sequence similarities to known toxins
 3. Coeliac disease
13. Genetic stability of the inserted/modified sequence
14. Homologous recombination / Horizontal Gene Transfer (HGT)



REQUIREMENTS COMPERA

Comparative

- 1.Choice of the comparator
- 2.Field trials description (including management practices)
- 3.Suitability of the test materials
- 4.Meteorological data
- 5.Experimental design of the studies in support of the comparative analysis
- 6.Germination study
- 7.Statistical analysis
 - 1.Agro/pheno
 - 2.Seed
 - 3.Forage



REQUIREMENTS COMPERA

ERA & PMEM Plan

1. General approach
2. Persistence and invasiveness including plant-to-plant gene flow
3. Plant to microorganism gene transfer
 1. HGT BI analysis
4. Interaction between the GM plant and target organisms
5. Interaction of the GM plant with non-target organisms (NTOs)
6. Impacts of the specific cultivation, management and harvesting techniques
7. Effects on biogeochemical processes
8. Effects on human and animal health
9. PMEM Plan



REQUIREMENTS FOOD & FEED

Food & Feed

1. Protein characterisation (e.g. mol/biochem)
2. Physicochemical and functional equivalence
3. Protein equivalence (in case of NEPs produced in binary system)
4. Stability in-vitro (Digestibility)
5. Stability in-vitro (influence of pH and T°)
6. 90d study
7. 28d study
8. IgE binding human sera (in case of NEPs from allergenic sources)
9. Endogenous allergens
10. Human nutrition
11. Animal nutrition
12. Human dietary exposure
13. Animal dietary exposure



RA AREAS IDENTIFIED BY EFSA (EFSA GMO PANEL, 2022)

From [EFSA GMO Panel \(2022\)](#):

- *Single first* principle challenging in case of high number of inserted/modified sequences
- Assessment of multiple novel proteins in case of high number of modifications / challenging for protein characterization-assessment
- History of Safe Use / Familiarity with the environment concepts
- Comparative approach challenging for genome-edited plants with complex trait



DISCUSSION

3 groups, each one discussing at least one case study

- Group 1: Case study 1
- Group 2: case study 2
- Group 3 (online participants): Case study 2

Questions to be answered:

1. What are the RA challenges for MC, COMPERA and FF areas using current RA requirements?
2. What are the RA areas that need further development and/or elaboration when assessing NGT plants?



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