Webinar | 19 December 2023

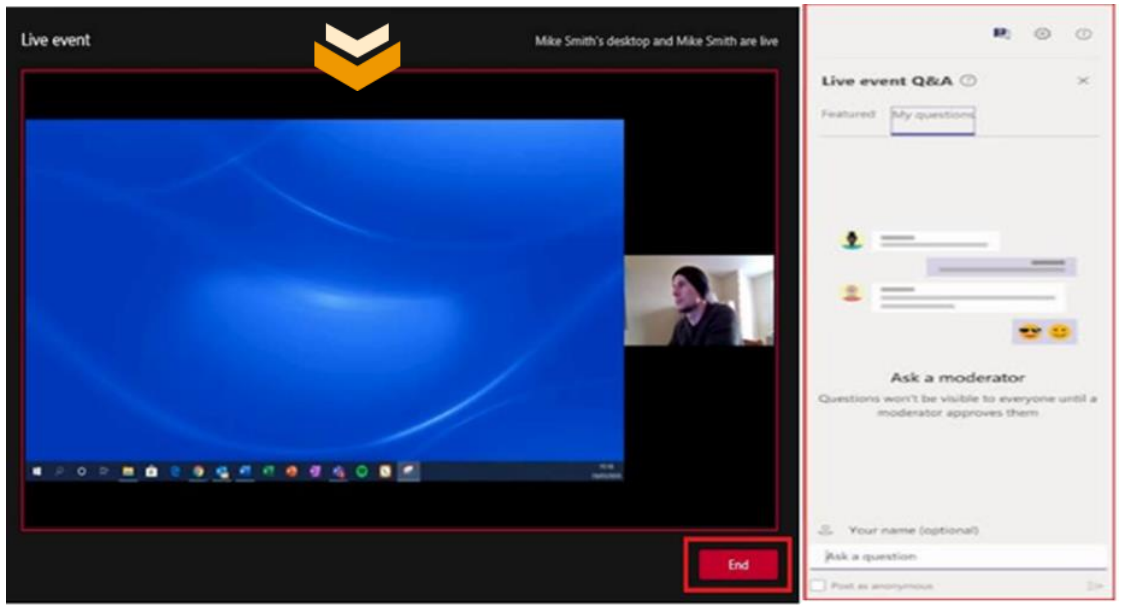
SELF-TASK MANDATE ON PROTEIN SAFETY ASSESSMENTS IN GMO

EUROPEAN FOOD SAFETY AUTHORITY

HOUSE KEEPING RULES

- You are **automatically connected** to the audio broadcast. One-way audio (**listen only** mode).
- **Scientific Questions, in English,** should be kept short and posted in the **Q&A chat;** we will try to aggregate and answer in the live Q&A session.
- If some questions remain unanswered you can resubmit them via the Ask a question Connect.EFSA tool (https://connect.efsa.europa.eu/RM/s/askefsa)
- This event is **being recorded** and recordings plus presentations will be published on EFSA's website

Presentation window



Q&A box: For any questions related to the topic or unexpected IT issues

AGENDA

Self-task mandate on protein safety assessment of GMO Panel

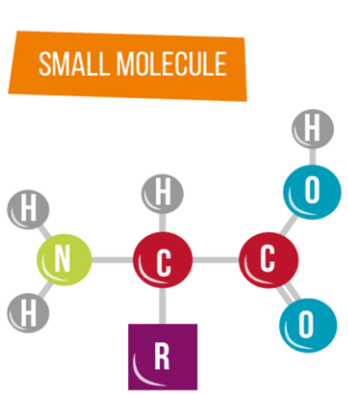
Open survey

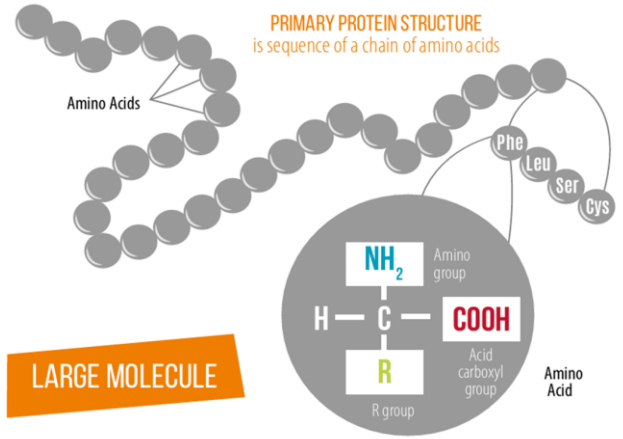
Questions

RISK ASSESSMENT OF GMOS – PROTEIN SAFETY

2003-2009

Adapted from chemical risk assessment





Need to improve and modernise protein safety assessments

BACKGROUND

Protein safety = protein toxicity and allergenicity

<u>Codex 2003-2009 defined the principles for the assessment</u>

- Regulation 503/EFSA GMO Guidance borrowed such principles
- Main information considered:
  1. Knowledge on the source/protein – HoSU
  2. Bioinformatics analysis
  3. *In vitro* studies
  4. *In vivo* studies

REGULATION 503 – PRESENT REQUIREMENTS

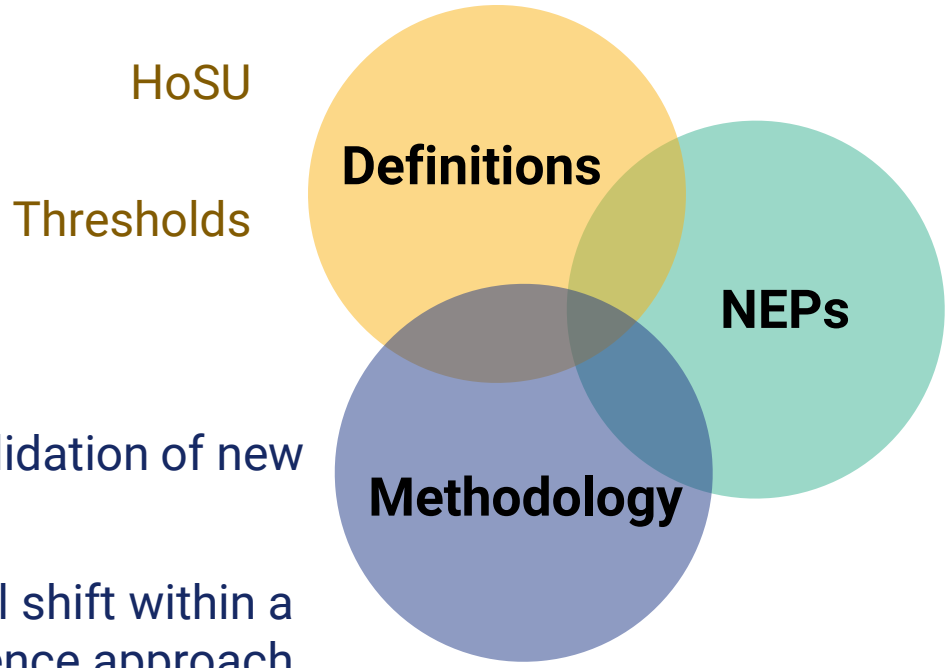
Toxicity assessment of newly expressed proteins (NEPs):

- Case by case approach. If history of safe consumption duly documented, specific tox-studies not needed
- Where specific testing is required, the applicant shall provide:
  - Molecular and biochemical characterisation of the NEP
  - Bioinformatics searching for homology to proteins known to cause adverse effects
  - Stability of the protein, e.g. influences of temperature, pH
  - Degradation of the NEP to proteolytic enzymes (pepsin test)
  - 28-day toxicity study, depending on outcome additional investigation may be needed

Allergenicity assessment of NEPs:

- Case by case approach. The approach shall include:
  - Bioinformatics searching for homology with known allergens
  - Specific serum screening, cases where there is a sequence homology or structure similarity and where the source of the gene is considered allergenic
  - Pepsin resistance and *in vitro* digestibility tests
  - Additional studies (cell-based, animal studies), if needed

EXPERIENCE GAINED



Similarity

HoSU

Thresholds

Proteins difficult to extract/purify (e.g. membrane-bound)

High number of proteins

Partial similarities to toxins/allergens

Standardisation and validation of new methods

Experimental shift within a weight-of-evidence approach

Need for alternative methods

EFSA GMO PANEL SELF-TASK MANDATE

What is the current situation?

- Codex Alimentarius and in EU, Regulation No 503/2013
- Safety assessment of NEPs follows a case-by-case approach
  - Toxicity and Allergenicity studies

    Protein characterisation, BI, stability, 28d tox study, serum screening
  - When HoSU is duly documented, specific studies might not be required

Which challenges are we facing?

- High number of new proteins that may also be difficult to characterise/test
  - Membrane-bound
  - Transcription factors

Which are the future opportunities?

- Improve current practices and provide complementary/alternative methods
  - Experience gained
  - New protein safety assessment methodologies

https://open.efsa.europa.eu/questions/EFSA-Q-2023-00664

WHAT WE TRY TO ACHIEVE? – TERMS OF REFERENCE

Scientific Opinion reflecting on current practice, challenges and future opportunities of protein safety in GMOs

1. Lessons learned from experiences in the assessment of newly expressed proteins in the last 20 years, including more recent complex cases

2. Building on the experience and issues identified, develop a critical appraisal of new methodologies available with the potential to be used as complementary/ alternative testing strategies to current methodologies described in legal frameworks

3. Road map for future implementation of such complementary/alternative methods in risk assessment strategies

4. Recommendations for further research to address methodological development needs

EXAMPLES - WHAT WILL BE DISCUSSED?

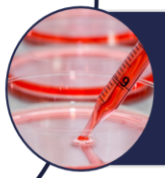
Weight of evidence approach Protein safety

- History of safety use
- Protein characterisation
- Mode of action
- Stability
- Source organism
- Phylogeny
- Structural/Functional similarity to known proteins
- Similarity to known toxins/allergens
- Fate in the gastrointestinal tract
- Interaction between proteins
- Others

Toxicological assessment	Tiered approach using *in vivo* studies only if concerns identified
Allergenicity assessment	Ranking of allergens[2] and post-market monitoring

New Approach Methodologies (NAMs) [3]

In silico tools: information on the derived structure of the novel protein



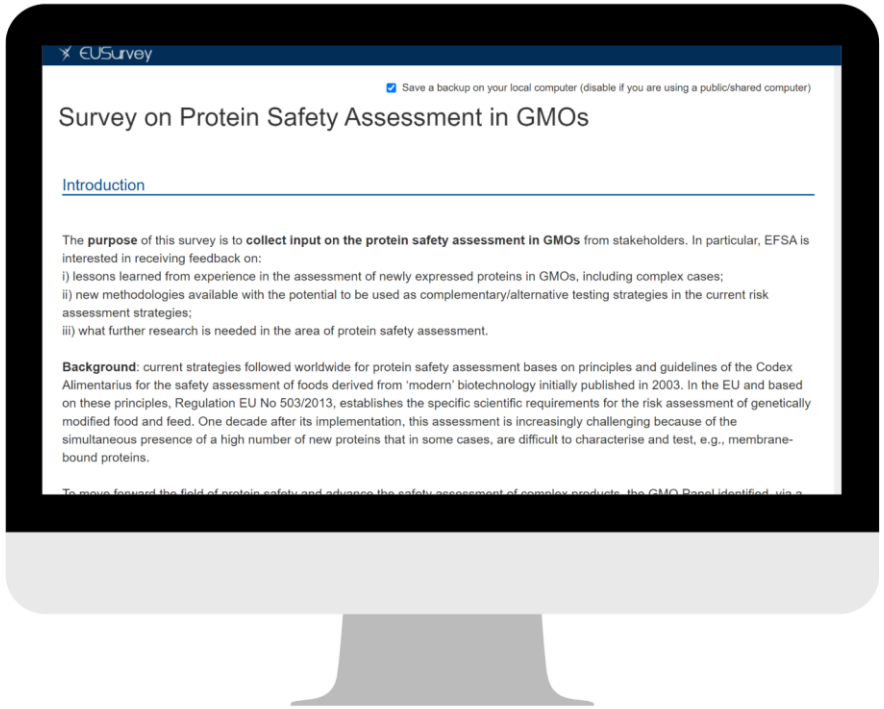
In vitro testing: stability tests could better inform about the fate of the novel proteins during processing, storage and after digestion in the gastrointestinal tract

EUROTOX 2023 – Toxicology letters – https://toxlet-384-s1.elsevierdigitaledition.com/

[2] EFSA GMO Panel, 2022. Scientific Opinion on development needs for the allergenicity and protein safety assessment of food and feed products derived from biotechnology. EFSA Journal 2022;20(1):7044

[3] Cattaneo et al., 2023. Implementing New Approach Methodologies (NAMs) in food safety assessments: Strategic objectives and actions taken by the European Food Safety Authority. Trends in Food Science & Technology, 133:277-290

SURVEY



- Open survey to collect input from stakeholders

Protein Safety Assesment_Survey_Link

SCAN ME

SURVEY

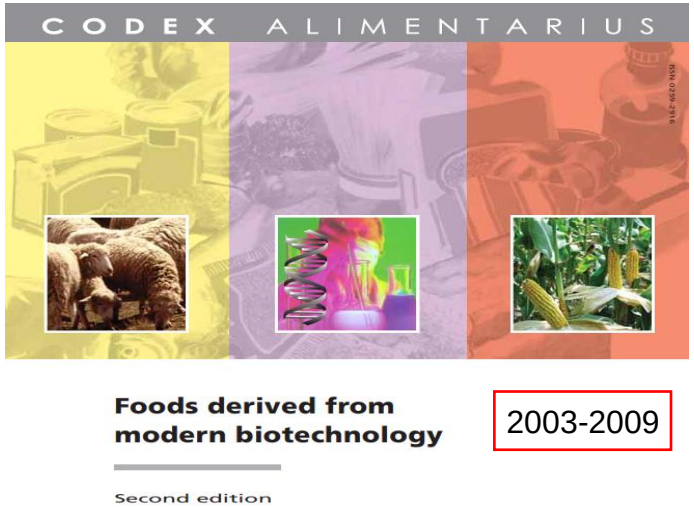
ToR1: Lessons learned from experiences in the assessment of newly expressed proteins in the last 20 years, including more recent complex cases

Q1. Which is the common strategy for the assessment of the new expressed proteins in GM food and feed?

Q.1.1. In how many cases/GMO Applications have the current methods identified issues/safety concerns for human/animal health?

Q.1.2. Do Risk Assessment Authorities request animal studies in addition to their basic/core requirements? What type?

Q.1.3. Which studies/methodologies have contributed most/least to identifying potentially adverse effects?



2003-2009

SURVEY

ToR1: Lessons learned from experiences in the assessment of newly expressed proteins in the last 20 years, including more recent complex cases

Q2. Which are the complex cases requiring a different approach for their assessment?

Q.2.1. What criteria can be used to consider a history of safe use of a newly expressed protein?

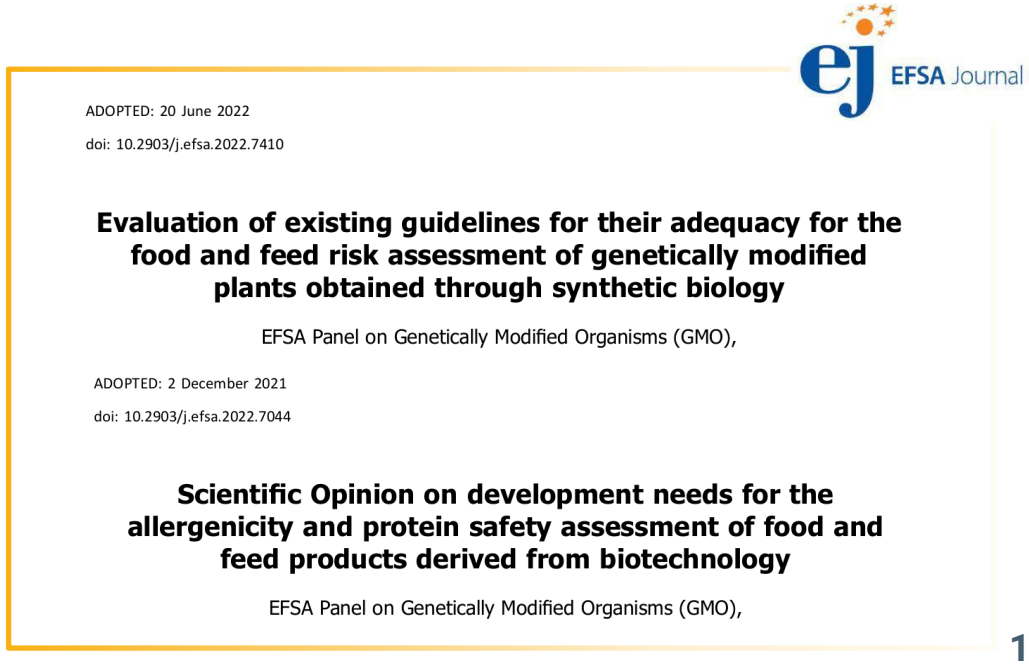
Q.2.2. Does each newly expressed protein have to be tested individually or are there also experiments/strategies that can be used to test proteins in combination?

High number of proteins to test

Proteins difficult to extract/purify

Partial similarity to toxins/allergens

Other cases



EFSA Journal

ADOPTED: 20 June 2022

doi: 10.2903/j.efsa.2022.7410

Evaluation of existing guidelines for their adequacy for the food and feed risk assessment of genetically modified plants obtained through synthetic biology

EFSA Panel on Genetically Modified Organisms (GMO),

ADOPTED: 2 December 2021

doi: 10.2903/j.efsa.2022.7044

Scientific Opinion on development needs for the allergenicity and protein safety assessment of food and feed products derived from biotechnology

EFSA Panel on Genetically Modified Organisms (GMO),

SURVEY

ToR2: Building on experience above and issues identified, a critical appraisal of new methodologies available with the potential to be used as complementary/alternative testing strategies to current methodologies described in legal frameworks.

Q1. Which complementary/alternative methodologies can be used for protein safety assessment, considering hazard identification and hazard characterisation?

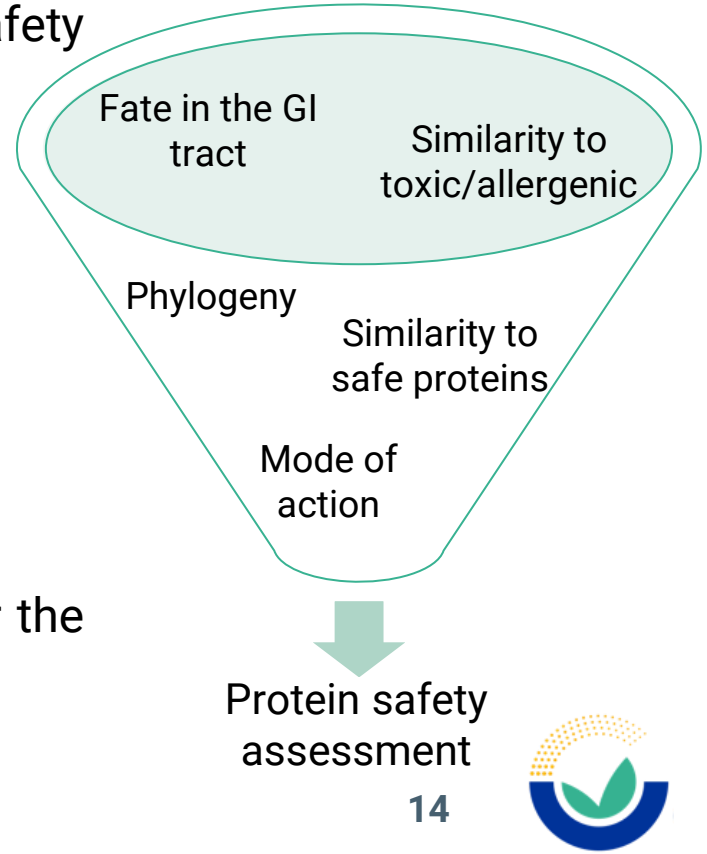
Q.1.1. Which new data sources / databases are needed?

Q.1.2. To what extent have the new methodologies been validated?

Q.1.3. Are new methodologies easy to use with the equipment and expertise readily available to most test facilities?

Q.1.4. Are new methodologies patent protected?

Q.1.5. Do they target specific aspects in a pathway and require other methodology to obtain a broad picture? If yes, are there other methods available?



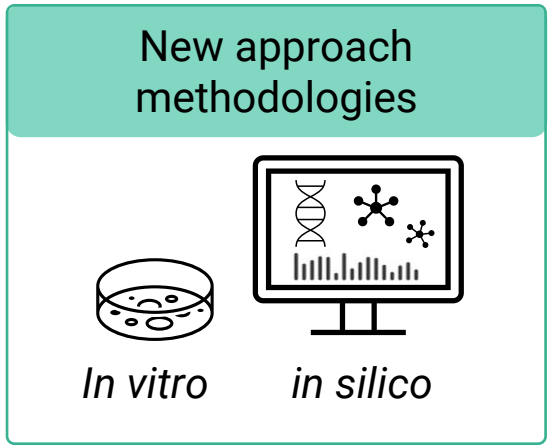
Q2. What stepwise approach following a weight-of-evidence should be used for the safety assessment of newly expressed proteins in GMOs?

SURVEY

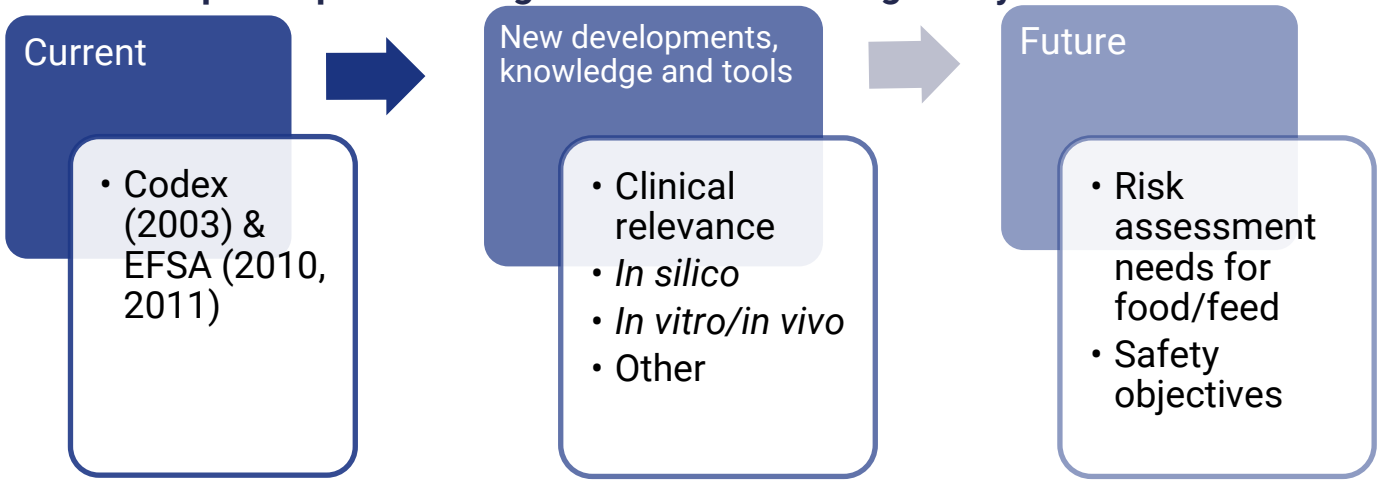
ToR3: Road map for future implementation of such complementary/alternative methods in risk assessment strategies

Q1. How these new methodologies can be introduced as complementary/alternative testing strategies in the overall weight-of-evidence approach for protein safety?

Q2. How should the outcome of these new methodologies be interpreted to inform the overall weight-of-evidence approach for protein safety?



Roadmap to improved 'Weight-of-Evidence' Allergenicity Risk Assessment



Adapted from https://www.efsa.europa.eu/en/efsajournal/pub/7044

SURVEY

ToR4: Recommendations for further research or for addressing methodological development needs

Q1. What are the main gaps and/or uncertainties in the protein safety assessment that would need to be addressed in the future?

Q2. What developmental and research activities are needed to address above gaps?

Q2.1. How would this change if tests in live animals were not performed or minimised?

Q3. What factors could be considered for building trust and confidence in these new methodologies?

Other: Additional comments not considered in previous questions

NEXT STEPS

Survey

Open until 18th Feb 2024

Public consultation

End June – mid September 2024

Adoption of the Scientific Opinion

End of 2024

EFSA Developmental projects (GMO-15 cluster)

Time to act by all parties involved

THANK YOU

TIME FOR QUESTIONS

ACKNOWLEDGMENTS

Moderator: Reinhilde Schoonjans

Speakers: Javier Moreno & Antonio Fernández

Scientific Support: Paschalina Grammatikou, Aina Gil González, Michele Ardizzone & Tilemachos Goumperis

Event organisation & engagement activities: Carolina Vastola and Margherita Guidi

Head of Unit: Ana Afonso

Please take few minutes to fill out the evaluation survey that you will receive after the event. Your feedback is essential to improve our future events.

THANK YOU FOR ATTENDING OUR EVENT

- The recording of today's event will be available on the EFSA website in few days
- In case we did not manage to answer all your questions, please feel free to re-submit them via EFSA Ask a question webform:

  EFSA.Connect at: https://connect.efsa.europa.eu/RM/s/askefsa

- You participation is welcomed for
  - the Survey (until 18 February), and
  - the public consultation (expected second half 2024) with scientific information on alternative methods will help the development of the EFSA GMO Panel opinion.

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