Request to provide scientific and technical assistance for a regular horizon scanning to assess new scientific data on plants, animals, microorganisms and products thereof obtained by new genomic techniques

18th GMO Network meeting

27/11/2024

EUROPEAN FOOD SAFETY AUTHORITY

TERMS OF REFERENCE

To regularly screen the scientific literature **to identify relevant studies** for the assessment of food and feed safety and the environmental safety of organisms and products obtained with **NGTs**, to **assess any new evidence** emerging from these studies, and to consider whether it may have implications for EFSA's relevant scientific opinions. A critical assessment of the quality and relevance of these studies should also be conducted, and regular reports delivered to the Commission.

1. Develop and validate **search strategies** to be used for searching of scientific literature databases with adequate sensitivity and specificity to identify studies that could be relevant as regards the safety, risk assessment and other considerations examined by EFSA in its relevant scientific opinions concerning NGTs applied to plants, micro-organisms and animals.
2. Develop and pilot **criteria for evidence inclusion and exclusion**, and **critical appraisal tools** to support the assessment of relevant published scientific evidence
3. **Extract and summarise relevant data and evidence** and assess whether any new data and evidence may have implications for EFSA relevant scientific opinions
4. Deliver **biannual reports** on relevant findings

MANDATE TIMELINE

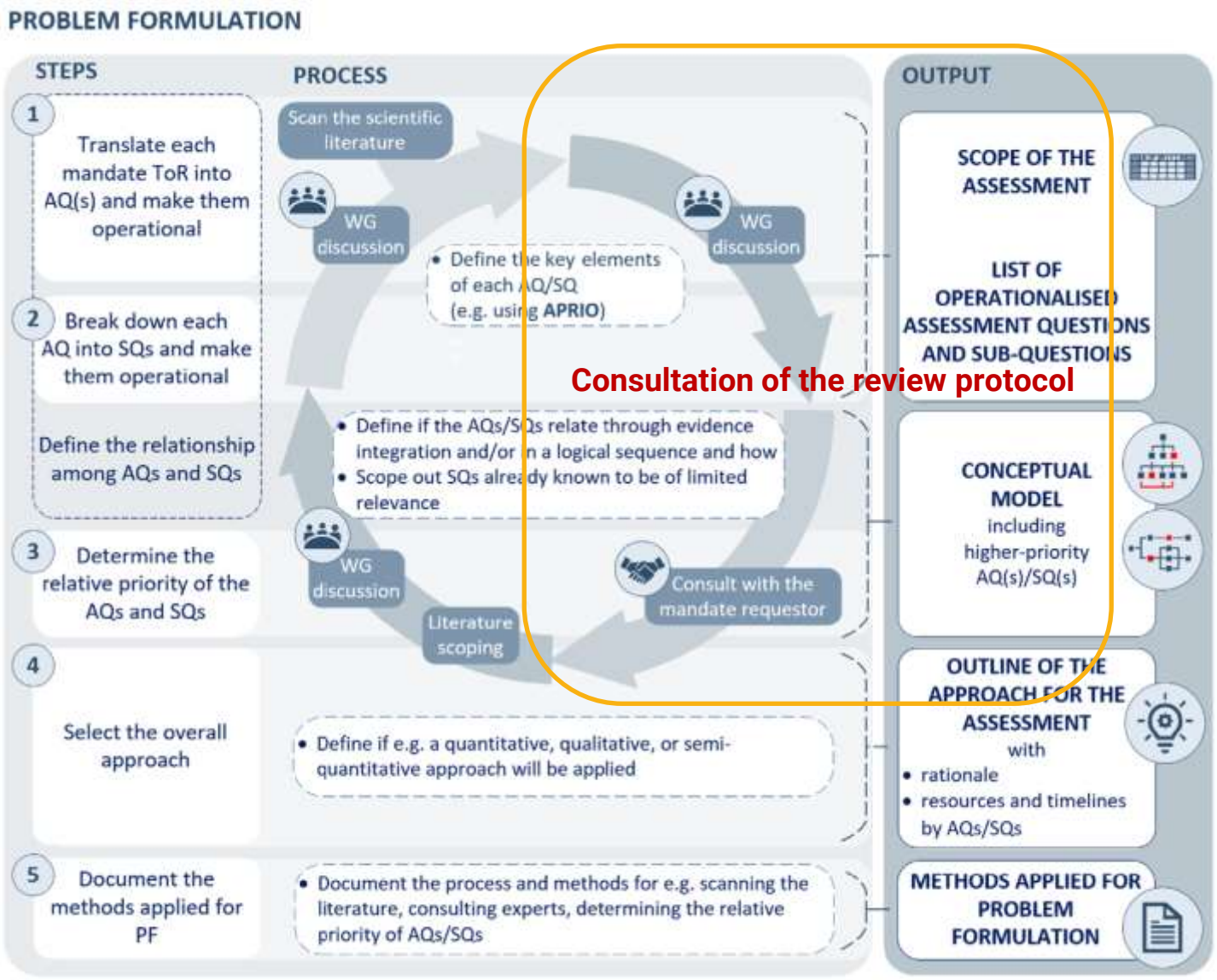
Mandate start: November 2024

1st deliverable: June 2025

Reviews every 6 months

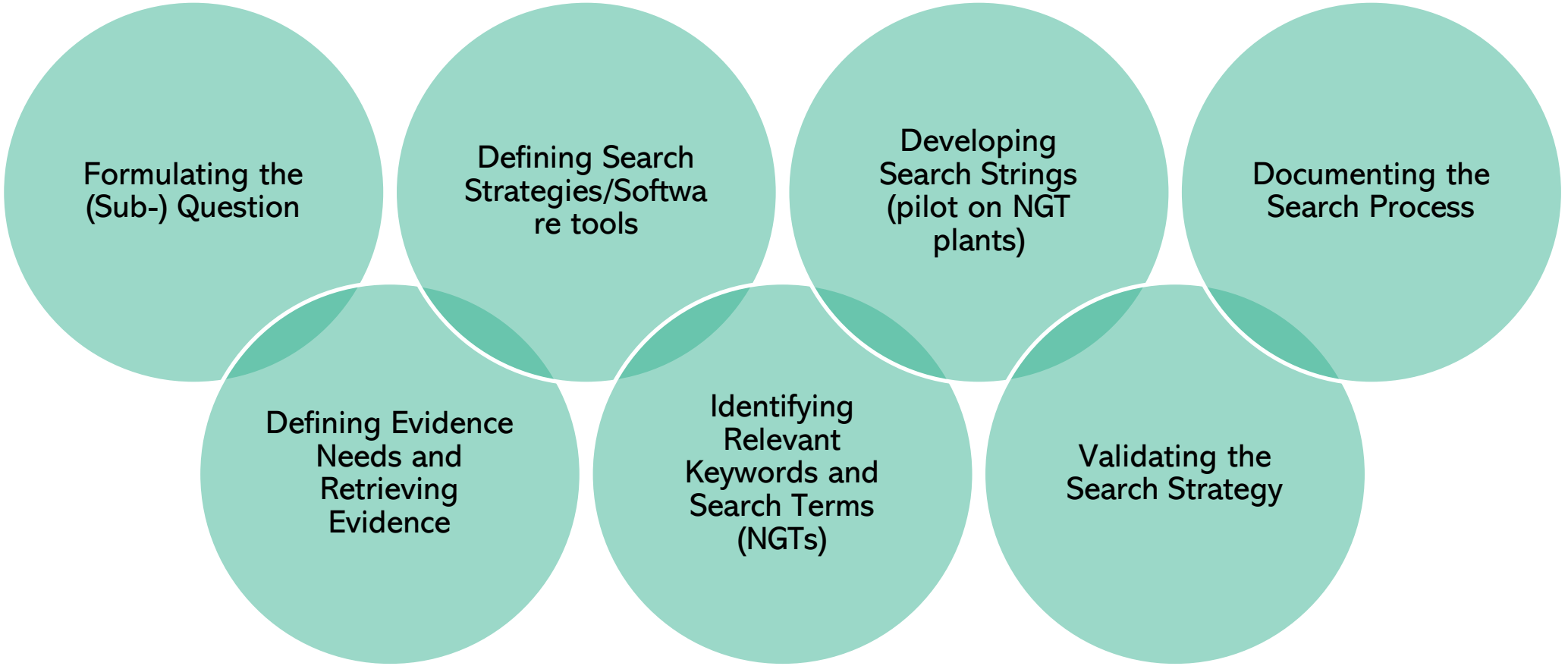
Mandate end: December 2026

PROTOCOL DEVELOPMENT STEPS

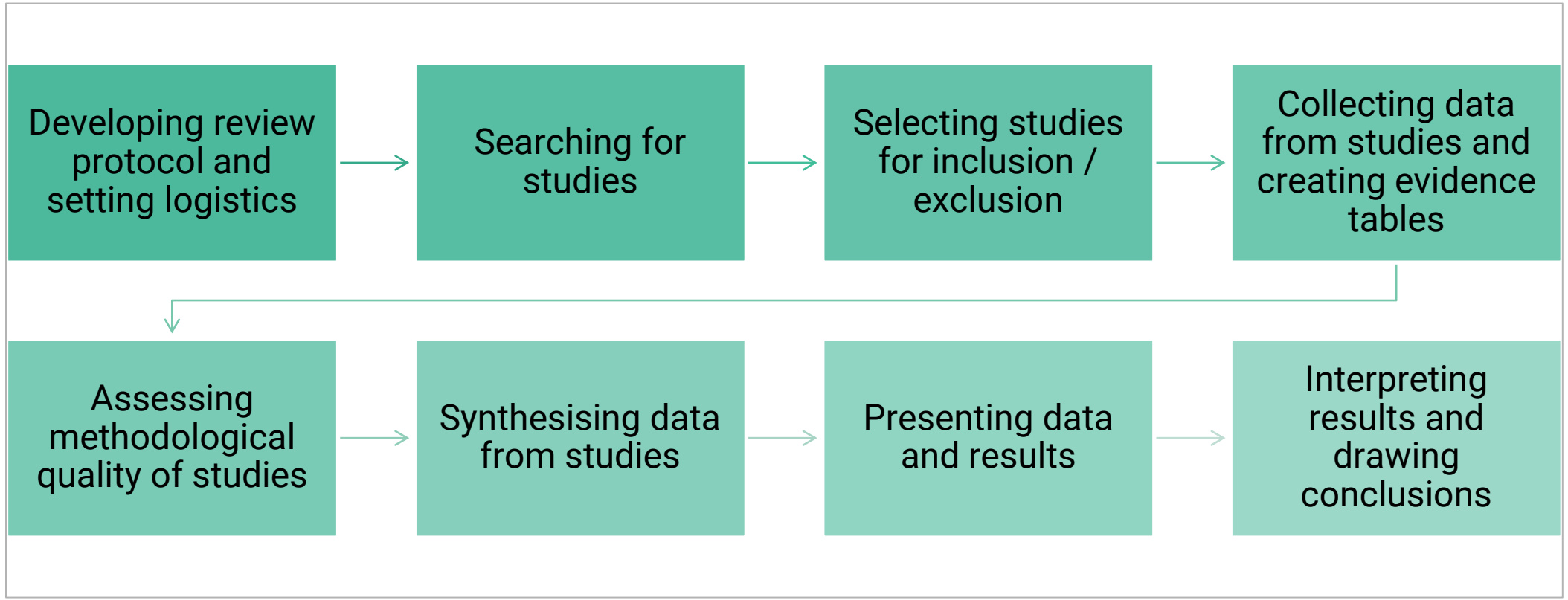


EFSA SC (EFSA Scientific Committee), More, S., Bampidis, V., Benford, D., Bragard, C., Hernández-Jerez, A. F., Bennekou, S.H., Koutsoumanis, K., Lambré, C., Machera, K., Mullins, E., Nielsen, S.S., Schrenk, D., Turck, D., Younes, M., Kraft, A., Naegeli, H., Tsaioun, K., Aiassa, E, … Halldorsson, T. I. (2023). Guidance on protocol development for EFSA generic scientific assessments. *EFSA Journal*, 21(10), 1–68. https://doi.org/10.2903/j.efsa.2023.8312

MAIN STEPS FOR CONDUCTING LITERATURE SEARCHES



SYSTEMATIC REVIEW WORKFLOW



European Food Safety Authority; Application of systematic review methodology to food and feed safety assessments to support decision making. *EFSA Journal* 2010; 8(6):1637. [90 pp.]. doi:10.2903/j.efsa.2010.1637

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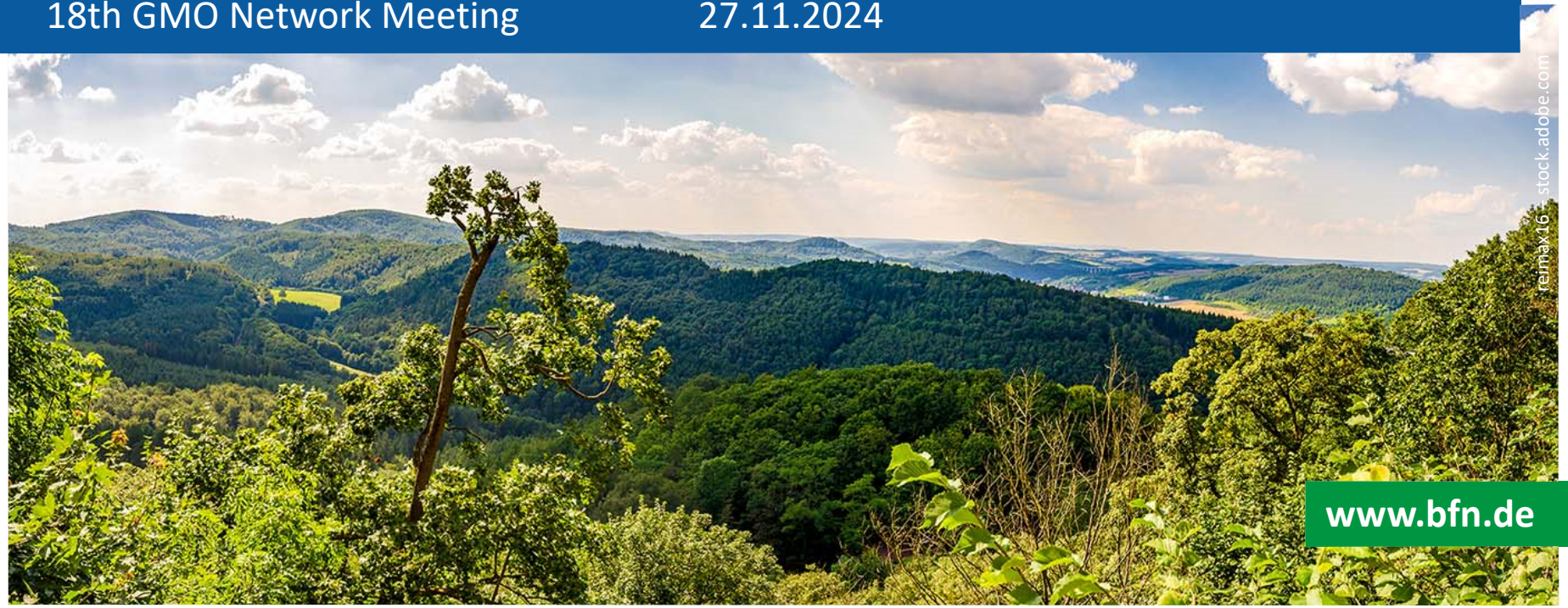
EUROPEAN FOOD SAFETY AUTHORITY

Federal Agency for Nature Conservation

New genomic techniques – BfN activities

Wolfram Reichenbecher – Division I 3.2 Assessment Synthetic Biology, Enforcement Genetic Engineering Act

18th GMO Network Meeting 27.11.2024



www.bfn.de

- To give an overview about R&D projects on NGTs commissioned by BfN
- To inform about outputs and recent publications
- From R&D and other projects (with/without BfN co-authorship)

Risk hypotheses regarding the environmental impact of genome-edited crops

- 05/2023 - 09/2025
  FGU (Project Genetic Engineering and the Environment)
- Update existing overviews of NGT applications and analyse possible ecological risks for relevant case studies
- Output: publications and fact sheets
  https://fachstelle-gentechnik-umwelt.de/en/project-descriptions-2023/

Koller and Cieslak (2023) ***A perspective from the EU: unintended genetic changes in plants caused by NGT—their relevance for a comprehensive molecular characterisation and risk assessment.***

Koller et al. (2024) ***Environmental risk scenarios of specific NGT applications in Brassicaceae oilseed plants****.*

Genome editing – new requirements for monitoring environmental impacts

- Finished project, division II 1.3 terrestrial monitoring
  Environmental Agency Austria
- Publication scrutinized whether existing concepts for GMO monitoring can be applied for novel types of GMOs
- GM microalgae, GM freshwater fish, and GM applications in fruit orchards as cases
- Specific monitoring requirements identified for novel GMO applications
- Additional surveillance activities have to be included in PMEM to detect potential adverse environmental effects

Dolezel et al. (2024): ***Challenges for the Post-Market Environmental Monitoring in the European Union Imposed by Novel Applications of Genetically Modified and Genome-Edited Organisms****.*

Alternative strategies for detectability and traceability of GMO products

- Finished project
  Öko-Institut and Environmental Agency Austria
- Comprehensive analysis of existing traceability systems for globally traded agricultural products, esp. soya.
- Analysis of legal requirements for traceability of imports in other sectors (timber, conflict minerals) and their traceability systems.
- Conclusions:
  - Findings from other sectors can be applied to products that may contain GMOs
  - Reversal of burden of proof is proposed, i.e. to follow a due dilligence approach

Teufel et al. (2024) ***Strategies for Traceability to Prevent Unauthorised GMOs (Including NGTs) in the EU: State of the Art and Possible Alternative Approaches***

Environmental effects of RNAi-based GM crops and methods for transient modification of organisms

- 07/2022 - 06/2025
  Fraunhofer Institute for Molecular Biology and Applied Ecology (IME)
- Project objectives
  - Scan the horizon for RNAi-based GM plants and other RNAi applications to classify trends in this field
  - Identify potential u.e. in RNAi-based GMPs on environment with focus on NTO
  - Survey biotech tools for transient modification of organisms and outline new challenges for regulation and RA.
- Output: three publications planed

Submitted: Germing et al. (2024) ***Crop protection by RNA interference – a review of approaches and current state of developments and use***

Operationalisation of technology assessment for GMOs

- 11/2023 - 07/2026
  Uta Eser, Büro für Umweltethik in Tübingen
- Project aims to give orientation for the assessment of GMOs (including NGT) beyond statutory risk assessment.
- Done by analysing of potential assessment aspects and available evidence.
- Several workshops involved
- Planed output: Handbook in Englisch and German

Genetically modified organisms in near-natural and natural ecosystems

- From 10/2024 - 08/2027,
  Environmental Agency Austria
- Project aims to investigate the ecological impacts when a GMO establishes in natural habitats and how they could be assessed prior to authorization.
- Three case studies: GM salmon, GM wasp and GM chestnut
- Three workshops and two publications planed

Horizon scanning synthetic biology, genetically modified microorganisms

- Q4/2024 – Q4/2027,
  Environmental Agency Austria
- Project aims to investigate the current state of knowledge for applying synthetic biology in microorganisms, algae and fungi (GMM) to support risk assessment and policy advice.
- Project involves workshops and in-depth interviews
- 1st WS on applications and risks of GMM
  with experts from research, industry and administration
- 2nd WS on using artificial intelligence for developing GMM
  with experts from microbiology, biotechnology, artificial intelligence and RA
- Output: webinars, final workshop, two publications and report

Selected publications

Publications from R&D projects with/without BfN co-authorship or from other projects

Bossert, L. N.; Potthast, T. (2024): Genetic Engineering, Nature Conservation, and Animal Ethics in advance. In: *Environmental Ethics*. https://doi.org/10.5840/enviroethics202442674

Dolezel, M.; Lang, A.; Greiter, A.; Miklau, M.; Eckerstorfer, M.; Heissenberger, A. et al. (2024): Challenges for the Post-Market Environmental Monitoring in the European Union Imposed by Novel Applications of Genetically Modified and Genome-Edited Organisms. In: *Biotech (Basel (Switzerland))* 13 (2). https://doi.org/10.3390/biotech13020014

Eckerstorfer, M.F.; Dolezel, M.; Miklau, M.; Greiter, A.; Heissenberger, A.; Engelhard, M. Scanning the Horizon for Environmental Applications of Genetically Modified Viruses Reveals Challenges for Their Environmental Risk Assessment. Int. J. Mol. Sci. 2024, 25, 1507. https://doi.org/10.3390/ijms25031507

Eckerstorfer et al. *(In preparation*). Environmental applications of GM microorganisms: Tiny critters posing huge challenges for risk assessment and governance

Germing, K.; Schiermeyer, A.; Hommen, U.; Zühl, L.; Eilebrecht, S.; Eilebrecht, E. (*Submitted*) Crop protection by RNA interference -a review of approaches and current state of developments and use. In: *Environmental Sciences Europe*

Hagen, K.; Otto, M.; Stracke, K..; Engelhard, M. (2024): Synthetic biology, genetic engineering in the wild, and biological diversity. In: Giersberg, Mona; Meijboom, Franck; Bovenkerk, Bernice (Hrsg.): Back to the future – Sustainable innovations for ethical food production and consumption. Brill, Leiden, NL, S. 391–397. https://doi.org/10.1163/9789004715509_064

Teufel, J.; Hernández, V. L.; Greiter, A.; Kampffmeyer, N.; Hilbert, I.; Eckerstorfer, M. et al. (2024): Strategies for Traceability to Prevent Unauthorised GMOs (Including NGTs) in the EU: State of the Art and Possible Alternative Approaches. In: *Foods* 13, Artikel 369. https://doi.org/10.3390/foods13030369

Koller, F.; Cieslak, M.; Bauer-Panskus, A. (2024): Environmental risk scenarios of specific NGT applications in Brassicaceae oilseed plants. In: *Environmental Sciences Europe* 36 (1). https://doi.org/10.1186/s12302-024-01009-1

Koller, F.; Cieslak, M. (2023): A perspective from the EU: unintended genetic changes in plants caused by NGT—their relevance for a comprehensive molecular characterisation and risk assessment. In: *Frontiers in bioengineering and biotechnology* 11:1276226. https://doi.org/10.3389/fbioe.2023.1276226

Miklau, M.; Burn, S.-J.; Eckerstorfer, M.; Dolezel, M.; Greiter, A.; Heissenberger, A. et al. (2024): Horizon scanning of potential environmental applications of terrestrial animals, fish, algae and microorganisms produced by genetic modification, including the use of new genomic techniques. In: *Front. Genome Ed.* 6, Artikel 1376927. https://doi.org/10.3389/fgeed.2024.1376927

Rabitz, F.; Giese, B.; Kelz, R.; Otto, M.; Potthast, T.; Quilodrán, C. S.; Teixeira, L. H. (2024): Putting gene drives into context: Risks, depth of intervention, and regulatory challenges. In: *GAIA* 33 (1), S. 165–169. https://doi.org/10.14512/gaia.33.1.9

Thank you for your attention!

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18th GMO network meeting

ROADMAP FOR ACTION ON THE APPLICATION OF OMICS AND ASSOCIATED BIOINFORMATICS APPROACHES IN RISK ASSESSMENT

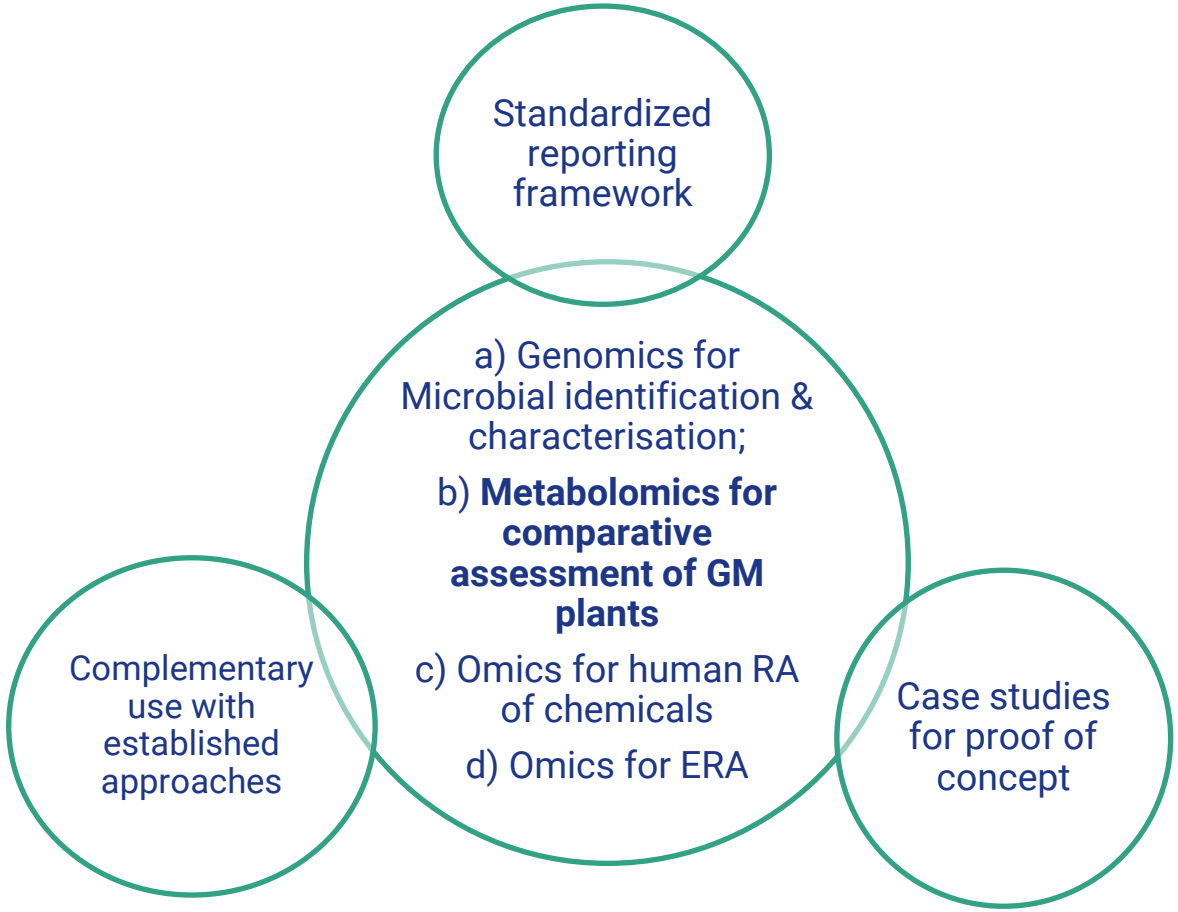
Konstantinos Paraskevopoulos (EFSA Chief Scientist Office)

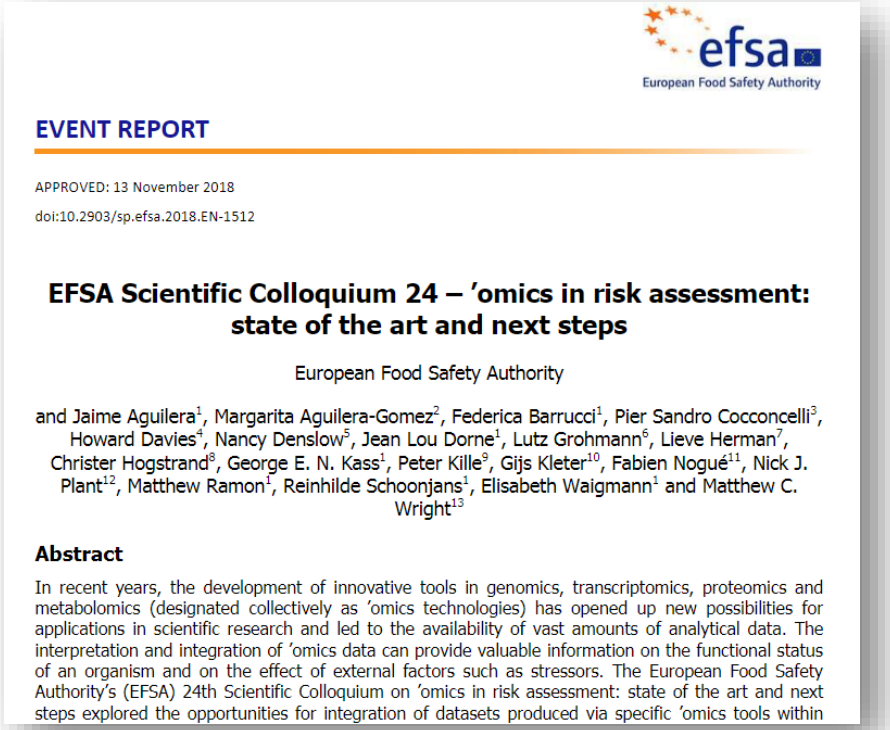
27 November 2024

EUROPEAN FOOD SAFETY AUTHORITY

EFSA SCIENTIFIC COLLOQUIUM 24

‘Omics in risk assessment: state of the art and next steps (2018)’: Integration of Omics in Risk Assessment (RA)





efsa
European Food Safety Authority

EVENT REPORT

APPROVED: 13 November 2018

doi:10.2903/sp.efsa.2018.EN-1512

EFSA Scientific Colloquium 24 – ’omics in risk assessment: state of the art and next steps

European Food Safety Authority

and Jaime Aguilera[1], Margarita Aguilera-Gomez[2], Federica Barrucci[1], Pier Sandro Cocconcelli[3], Howard Davies[4], Nancy Denslow[5], Jean Lou Dorne[1], Lutz Grohmann[6], Lieve Herman[7], Christer Hogstrand[8], George E. N. Kass[1], Peter Kille[9], Gijs Kleter[10], Fabien Nogué[11], Nick J. Plant[12], Matthew Ramon[1], Reinhilde Schoonjans[1], Elisabeth Waigmann[1] and Matthew C. Wright[13]

Abstract

In recent years, the development of innovative tools in genomics, transcriptomics, proteomics and metabolomics (designated collectively as ’omics technologies) has opened up new possibilities for applications in scientific research and led to the availability of vast amounts of analytical data. The interpretation and integration of ’omics data can provide valuable information on the functional status of an organism and on the effect of external factors such as stressors. The European Food Safety Authority’s (EFSA) 24th Scientific Colloquium on ’omics in risk assessment: state of the art and next steps explored the opportunities for integration of datasets produced via specific ’omics tools within

EFSA Scientific Colloquium 24 – 'omics in risk assessment: state of the art and next steps

EFSA ROADMAP FOR ACTION ON APPLYING OMICS AND BIOINFORMATIC APPROACHES

TECHNICAL REPORT

APPROVED: 05 September 2021

doi:10.2903/sp.efsa.2022.e200506

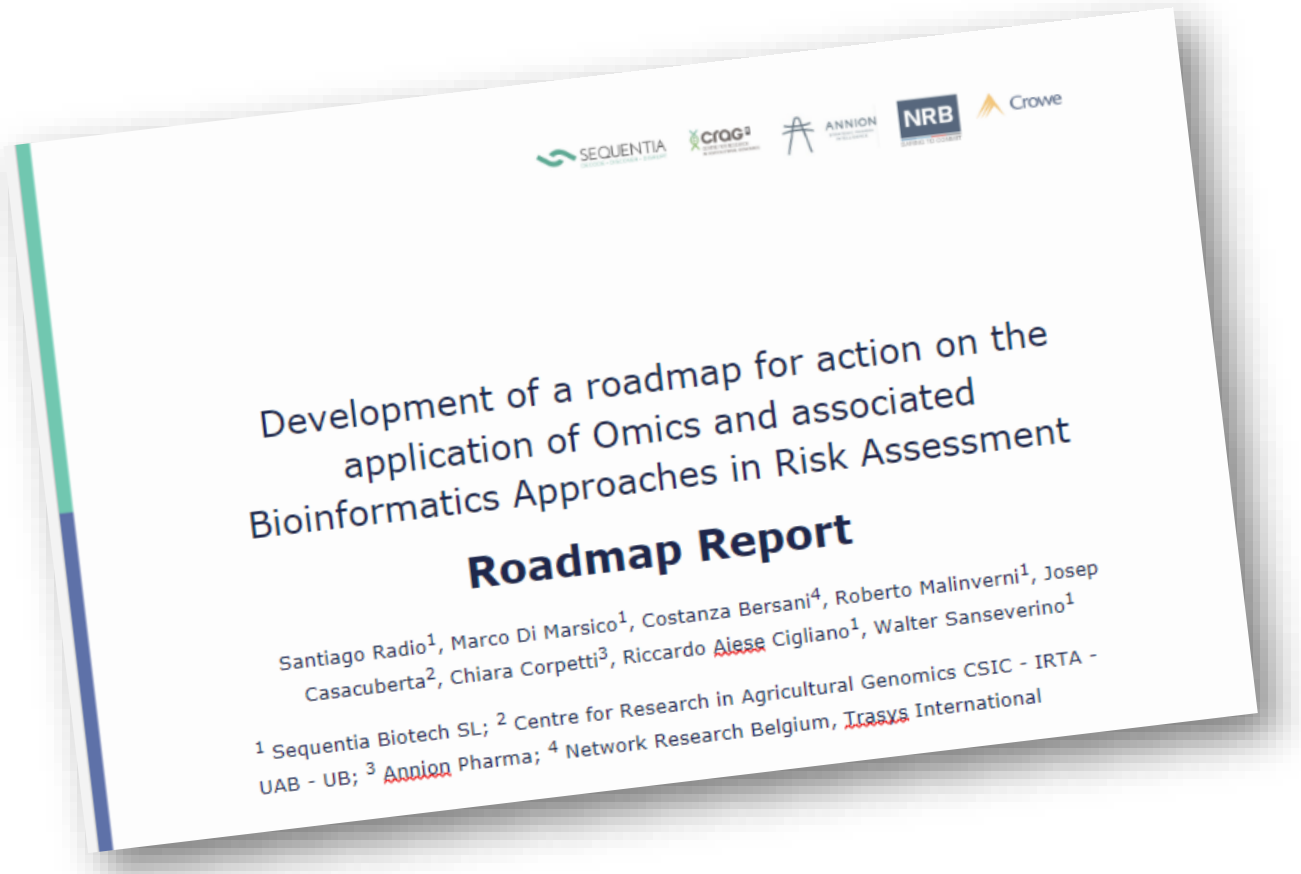
Theme (Concept) paper - Application of OMICS and BIOINFORMATICS Approaches: Towards Next Generation Risk Assessment

European Food Safety Authority (EFSA), Giovanni Iacono, Beatriz Guerra, George Kass, Konstantinos Paraskevopoulos, Juliane Kleiner, Claudia Heppner, Marta Hugas

https://efsa.onlinelibrary.wiley.com/doi/epdf/10.2903/sp.efsa.2022.e200506

EFSA's strategic objective

- By 2030 to routinely apply omics and associated bioinformatic approaches in risk assessment (RA)
- RA that will be leaner, automated and based on the mechanisms behind adverse effects , greatly enhancing EFSA's ability to assess food/feed related hazards and risks



Development of a roadmap for action on the application of Omics and associated Bioinformatics Approaches in Risk Assessment

Roadmap Report

Santiago Radio[1], Marco Di Marsico[1], Costanza Bersani[4], Roberto Malinverni[1], Josep Casacuberta[2], Chiara Corpetti[3], Riccardo Aiese Cigliano[1], Walter Sanseverino[1]

[1] Sequentia Biotech SL; [2] Centre for Research in Agricultural Genomics CSIC - IRTA - UAB - UB; [3] Annion Pharma; [4] Network Research Belgium, Trasys International

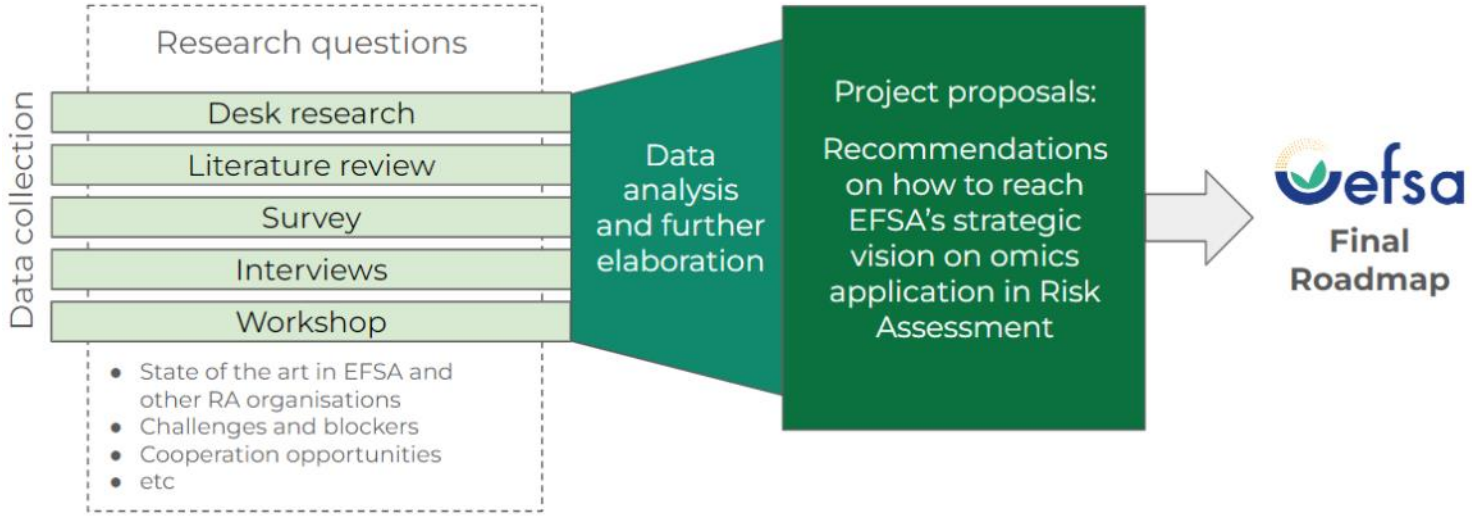
Links to documents

EFSA Roadmap report

Omics concept paper

ROADMAP STRUCTURE

Methodology



Roadmap output

- Understand **state of the art in omics** and bioinformatic-related approaches
- **Current work**, **initiatives** and **projects** of regulatory bodies for use of omics and bioinformatics tools **in RA**
- Identify **knowledge gaps** and potential areas of investment
- **Challenges and blockers** in the integration of omics in RA

SCOPE

Area 1
Plant Health

Area 2
GMOs

Area 3
Food Improvement Agents, Feed Additives, and FCM

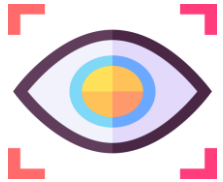
Area 4
Foodborne Zoonotic Microorganisms

Area 5
Animal Health & Welfare

Area 6
Food and Feed Contaminants

Area 7
Nutrition, Novel food and Nanotechnology

Scientific domains X **5 Risk Assessment Development Areas** X **Many OMICs**

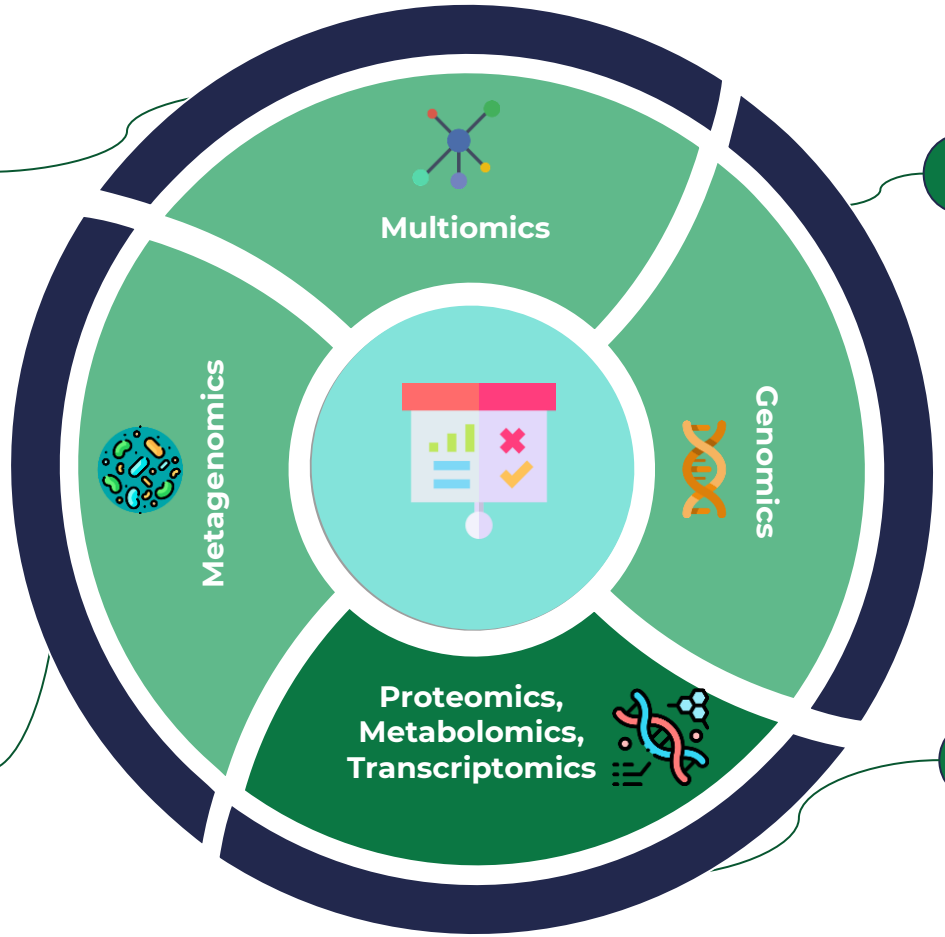


MAPPING AND KNOWLEDGE GAPS

4

Promising for elucidating complex molecular relationships in regulatory science.

Not identified use in regulatory science, but growing use in research.



1

WGS information is used by EFSA for foodborne outbreak investigation and for regulated-products.

Non harmonised use of powerful hybrid squencing apporaches

3

Globally recognized for its potential to aid the RA process.

No legal requirements (and no guidance) in food law to consider microbiomes in risk assessments.

2

Recognised for potential in chemical RA, supported by EFSA, EU projects, and OECD efforts.

Increasing use in EFSA RA, though not yet routine.

CHALLENGES AND BLOCKERS

General challenges and blockers that currently hamper an effective and efficient application and development of omics and bioinformatics approaches in EFSA Risk Assessment, and that were taken into account when designing the project proposals.

- **Lack of standardisation, validation and harmonisation**
- **Poor data integration**
- **Lack of advanced skills among relevant stakeholders**
- **Data access and sharing**
- **Regulatory constraints**
- **Lack of RA guidelines**
- **Lack of reference & updated databases**
- **Lack of case studies**
- **Lack of openly accessible detailed methods**

OVERVIEW OF THE RECOMMENDATIONS

01

Harmonisation of Hybrid Sequencing and Bioinformatics Approaches

Readiness level: **High**

02

Utilising Public Omics Repositories and Machine Learning Models to Infer Chemical Groupings

Readiness level: **Moderate**

03

Metagenomics Adoption in EFSA Risk Assessment

Readiness level: **Moderate-Low**

04

Omics-Based Risk Assessment of GM Plants

Readiness level: **Moderate**

05

Allergenicity Assessment of Novel Foods

Readiness level: **Moderate High**

06

Omics Data Analysis Platform Development

Readiness level: **High**

OMICS-BASED RISK ASSESSMENT OF GM PLANTS

Aim: Assessing **omics potential for complementing/substituting elements in the RA of GM plants; e.g. for measuring expression** of inserted/modified sequences and **profiling for comparative assessments**.

Current challenge

- Current RA approaches rely on limited endpoints
- Emerging complex GM plants present new challenges and may require more comprehensive evaluation
- Lack of standardised Omics implementation protocols in regulatory frameworks hinders their routine adoption

Objectives

- Implement proof-of-concept case studies integrating transcriptomics, proteomics, and metabolomics for holistic safety evaluation
- Develop & validate advanced statistical frameworks for comprehensive omics data interpretation
- Establish standardised protocols and quality measures to ensure reproducibility

OMICS-BASED RISK ASSESSMENT OF GM PLANTS

Aim: Assessing **omics potential for complementing/substituting elements in the RA of GM plants; e.g. for measuring expression** of inserted/modified sequences and **profiling for comparative assessments**.

Actions

- Organize a scientific colloquium on omics in GM plant risk assessment
- Develop suitable case studies to generate and analyse omics data for comparative assessment
- Create standardised protocols and quality metrics
- Engage with regulatory agencies to develop RA frameworks for omics data integration

Expected Impact

- Enhanced detection of unintended effects through comprehensive molecular profiling
- Improved evaluation capabilities for next-generation GM plants with complex modifications

ALLERGENICITY ASSESSMENT FOR NOVEL FOODS

Aim: Fill **knowledge gaps in allergenicity assessment** for novel foods using **untargeted proteomics to identify proteins** that may pose allergenic risks, with **potential applicability to GMOs.**

Current Challenge

- Traditional RA methods inadequate for novel proteins with different protein structures & post-translational modifications
- Complex mixtures, environmental and processing factors affect allergenicity evaluation
- Regulatory gaps and lack of standardized procedures for novel food assessments

Objectives

- Implement Untargeted shotgun proteomics for comprehensive protein profiling and find potential allergenic risks
- Develop advanced *in silico* methods (e.g., structural modeling, machine learning) to predict allergenic potential
- Standardise proteomics methodologies for regulatory acceptance

ALLERGENICITY ASSESSMENT FOR NOVEL FOODS

Aim: Fill **knowledge gaps in allergenicity assessment** for novel foods using **untargeted proteomics to identify proteins** that may pose allergenic risks, with **potential applicability to GMOs.**

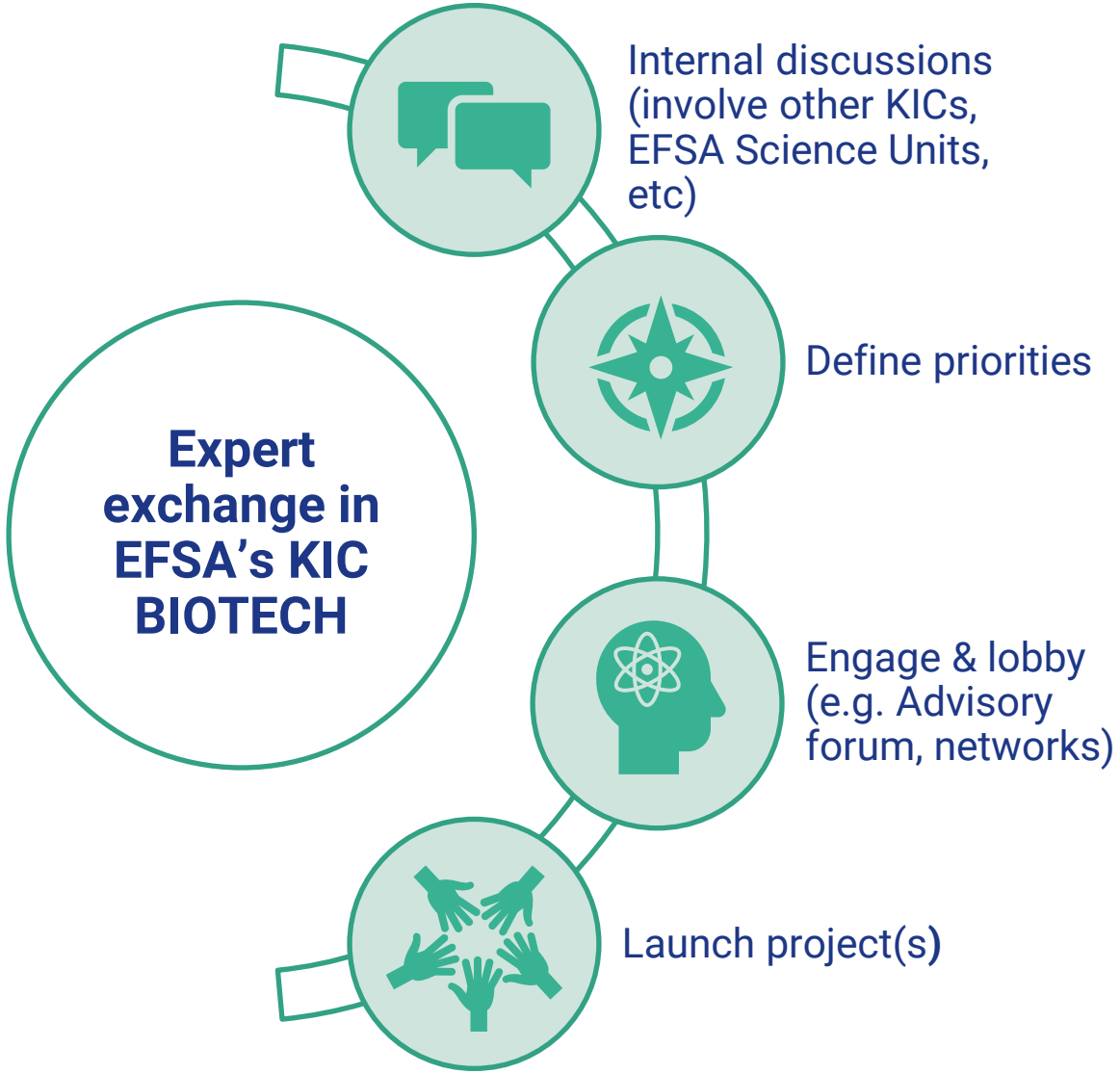
Actions

- Conduct literature review and case study(ies) selection
- Perform proteomic analysis of novel foods
- Predict allergenicity using computational tools
- Validate predictions experimentally
- Disseminate findings and engage with the public

Expected Impact

- Enhanced detection of potential allergens in novel foods
- Improved standardization of proteomic methods in risk assessment
- Strengthened consumer protection through advanced assessment

NEXT STEPS


Expert exchange in EFSA's KIC BIOTECH
Internal discussions (involve other KICs, EFSA Science Units, etc)
Define priorities
Engage & lobby (e.g. Advisory forum, networks)
Launch project(s)

DISCUSSION QUESTIONS

1) Looking at future GM plant risk assessment: do you see a need/opportunity to incorporate omics approaches, or are current methods sufficient? What added value would omics bring to safety assessment?
2) If we move towards implementing omics in GM plant risk assessment, what do you consider the main technical and regulatory obstacles/challenges that would need to be overcome?"

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Ministry of
Social Affairs and Health

Tackling challenges in recycling GMM fermentation waste

Kirsi Törmäkangas
Ministerial Adviser
27.11.2024

Introduction

- Providing biological waste for landfilling is not permitted any more
- Circular economy is favoured to reduce material use and CO^2 emissions
- Waste should be preferably handled near the production site (however, environmental licences and the production plant plot sizes may limit handling large amounts of waste on site)
- -> recycling opportunities are attractive for companies
- Marketing of a recycled end product derived from GMMs is challenging:
  - the end product cannot contain viable GMMs – otherwise the producer must apply for a marketing authorisation under Part C of Directive 2001/18/EC
  - companies have no appetite for Part C notifications (costs vs. market value) and Article 16 of Directive 2001/18/EC on specified GMOs has never been applied

Our experiences on recycling GMM fermentation waste

- Our own experiences all concern food/feed enzyme production plants (pharmaceutical production would be different)
- Large scale production with fungal or bacterial GRAS status production strains genetically modified to efficiently produce endogenous or exogenous enzymes (either secreted or intracellularly)
- GMM risk class 1 > inactivation of GMMs in contaminated material and waste, including those in process effluent before final discharge is optional (Directive 2009/41/EC)
- Enzyme purification process typically yields large amounts of GMM waste mass possibly including kieselguhr (diatomaceous earth) or other substances used for filtering

Properties of typical GMM fermentation waste

- Wet > not suitable for incineration; drying energy consuming (CO^2 emissions)
- High nitrogen content > not suitable for incineration (hazardous emissions)
- Heavy > not suitable for autoclaving, CO^2 emissions when transporting
- Kieselguhr > inorganic (not ideal for burning), increases waste mass

-> Environmental friendly solutions for handling (preferably on site):

- composting (mixed with other organic material)
- anaerobic fermentation (kieselguhr?)
- BUT… GMO legislation?

Solving the challenges – two case studies

- **Case 1:** Company A had the possibility to inactivate their GMM waste inside the production plant > no problem with composting after the Company A had confirmed that their GMM inactivation process works adequately
- **Case 2:** Company B did not have a possibility to inactivate their GMM waste inside the plant, nor a big enough plot to test the composting process on site
  - B suggested to combine efforts with Company C which recycles organic waste to produce mulch and fertilizers for consumers > testing composting on the production site of C
  - Does Dir 2001/18/EC apply? No, inactivation of Class 1 GMM waste is optional and previously it could be transported to landfill sites. C is not producing, using or storaging GMMs, but aiming to inactivate them.
  - Does the composting process of C really inactivate the remaining GMM:s in the waste?
  - How to verify it?

Risk assessment and management issues considered in Case 2

- Properties of the GMMs affecting survival in the composting process:
  - temperature sensitivity
  - auxotrophies
  - capability to form spores
  - possible toxins etc.
- Composting process:
  - total lenght
  - maximum temperatures and their time span
  - compound mixture
  - lime precipitation
  - hygienisation steps etc.

Further steps in Case 2

- Company B (in collaboration with C) was required to test for two years that the two-phased tunnel composting process of C including lime precipitation process was sufficient to inactivate the GMM strains.
- Not easy to determine the amount, frequency and specifics of sampling!
- During the test period B was able to verify that the composting process reliably inactivates their GMM strains.
- Final decision of the Finnish CA: No obligations under Directive 2001/18/EC, provided that B and C continue self-monitoring the composting process. If the temperatures or pH are below those achieved during the test period, the compost batch cannot be used for products to be marketed.

Questions

- Did we miss something in the assessments?
- Did we miss some obvious solution to the legal / practical problems?
- Any general ideas on taking and analysing samples from a composting process to verify the presence of viable GMOs or spores thereof? (details must of course be decided case by case, and PCR is not suitable)
- If the end products of GMM waste recycling could be used in plant cultivation, is there a need for further risk assessment guidance? If so, for which situations?

Thank you!

Ministry of
Social Affairs and Health

EC mandate M-2018-0205: NGTs applied to animals for agri food and feed uses

GMO network

November 2024

EUROPEAN FOOD SAFETY AUTHORITY

Scientific opinion on NGT animals – what it is not

is not a guidance

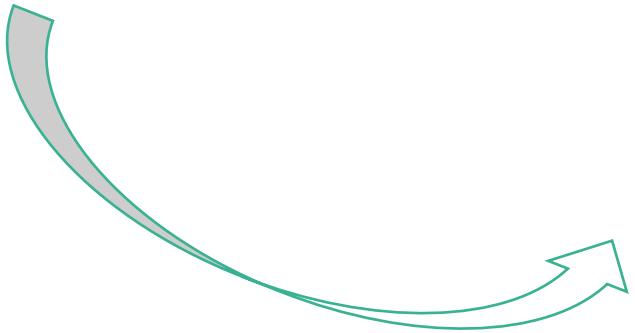
Scientific opinion on NGT animals – what it is

Scientific opinion about the readiness to assess a dossier on NGT animals by EFSA, should it arrive for the first time in EU

EC mandate M-2018-0205 - Knowledge gathering

ToR1 - Knowledge gathering on known cases of animals, and their food and feed products, obtained by new developments in biotechnology

- ❑ identify animals and their products obtained by new development in biotechnology described since 2001 including their traits and uses
- ❑ list the techniques and modifications used, including explanation of relevant terminology
- ❑ identify animals and their products developed since 2001 that are subject to authorisation procedures by international authorities, and the corresponding available risk assessments (e.g. opinions, guidances, authorizations) that exist
- ❑ *collect per case the data and information relevant for risk assessment, and structure it according to the EFSA guidances*

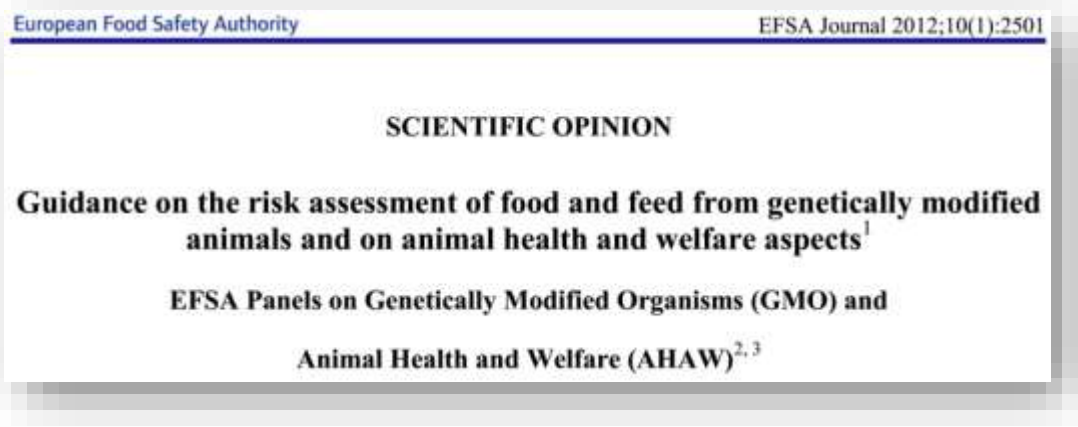


Van Eenennaam, A.L. 2023.
New genomic techniques (NGTs) animals and their agri/food/feed products.
EFSA supporting publication 2023:EN-8311. 82 pp. doi:10.2903/sp.efsa.2023.EN-8311

EC mandate M-2018-0205 - Scientific opinion

Opinion on potential novel hazards/risks from new developments in biotechnology applied to current and near market animals and adequacy of the current EFSA risk assessment guidance, covering all aspects of molecular characterisation, food feed safety & welfare, and environmental impact.

- ❑ identify, where possible, novel potential hazards and risks which new developments in biotechnology applied to current or near market animals could pose for humans, animals and the environment compared to conventional breeding or established techniques of genetic modification
- ❑ determine whether the existing guidelines* for risk assessment of genetically modified animals are applicable, fully or partially, adequate and sufficient to risk assess new developments in biotechnology applied to animals
- ❑ identify on which specific areas and aspects existing guidelines* should be updated, adapted or complemented in case existing guidelines for risk assessment are considered not applicable, partially applicable, not adequate or not sufficient



Structure of the scientific opinion

Abstract Keywords Summary	
1	**Introduction**
1.1	Background and Terms of Reference as provided by the requestor
1.1.1	Background
1.1.2	Terms of Reference as provided by the requestor
1.2	Interpretation of the Terms of Reference
1.3	Additional information to set the scene for the execution of the EC Mandate
1.3.1	Definitions and concepts applicable to the scope of the mandate
1.3.2	New developments in biotechnology applied to animals
1.3.3	Methodologies used in EFSA for the animal welfare risk assessment
1.3.4	Risk assessment of gene edited animals through different developmental stages
2	**Data and Methodologies**
2.1	Knowledge gathering on known cases of NGT animals
2.2	Ad hoc expert Working Group and its methodology, and existing guidelines
2.3	Selection of case studies
2.4	Consultations
3	**Assessment**
3.1	Novel potential hazard and risk identification
3.2	Evaluation of the applicability and sufficiency of the EFSA GMO and AHAW Panel, 2012
3.3	Evaluation of the applicability and sufficiency of EFSA GMO Panel, 2013
4	**Specific areas and aspects of the EFSA guidance documents which should be updated, adapted or complemented**
4.1	EFSA GMO and AHAW Panel, 2012
4.2	EFSA GMO Panel, 2013
5	**Conclusions**
6	**Recommendation**
7	**References**
Appendices Annexes Glossary	

Way forward to finalization

GMA-NGT WG
Work in progress toward finalization of the Draft opinion

GMA-NGT WG
Work in progress toward finalization of the Final opinion

Sep 2024 | Nov 2024 | Dec 2024 | early 2025 | Feb/May 2025 | Jun/Jul 2025

GMO Panel (open)
Discussion on the draft opinion

GMO Panel
Endorsement of the draft opinion

Public consultation on the draft scientific opinion

Webinar to introduce the PCs

GMO Panel
Adoption of the scientific opinion

efsa JOURNAL

Thank you for your attention

Scientific Opinion on **newly expressed proteins** in GMO risk assessment

Updates

EUROPEAN FOOD SAFETY AUTHORITY

PROTEIN SAFETY - TOXICITY & ALLERGENICITY OF NEPS

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

1. Lessons learnt from experiences in the assessment of Newly Expressed Proteins in the last 20 years, including more recent complex cases
2. Building upon 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. Roadmap for future implementation of complementary/alternative methods in risk assessment strategies
4. Recommendations for further research to address methodological development needs

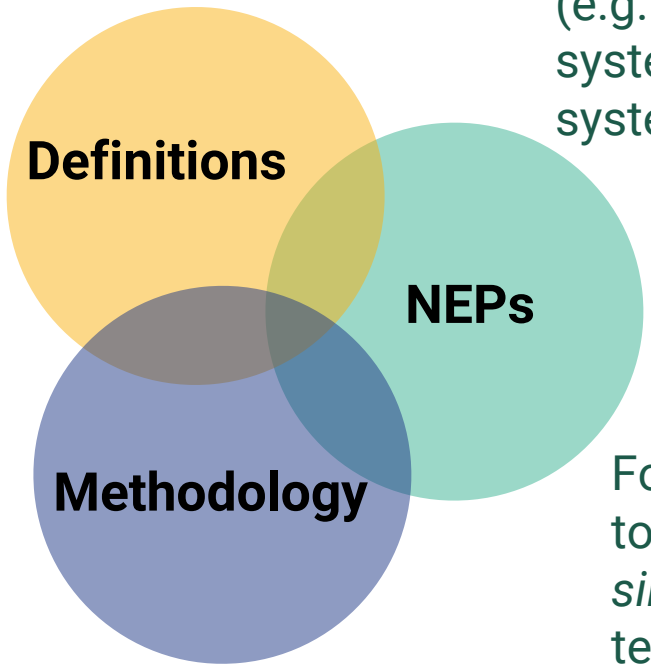
WHY investing on this topic?

FROM EXPERIENCE GAINED – ADDITIONAL NEEDS

Similarity

HoSU

Thresholds



For proteins difficult to extract/purify (e.g. membrane-bound): purification systems or alternative expression systems

For high number of proteins: agreement on testing the mixture or testing each individually

For proteins with partial similarities to toxins/allergens: more targeted *in silico* tool or hypothesis driven *in vitro* tests

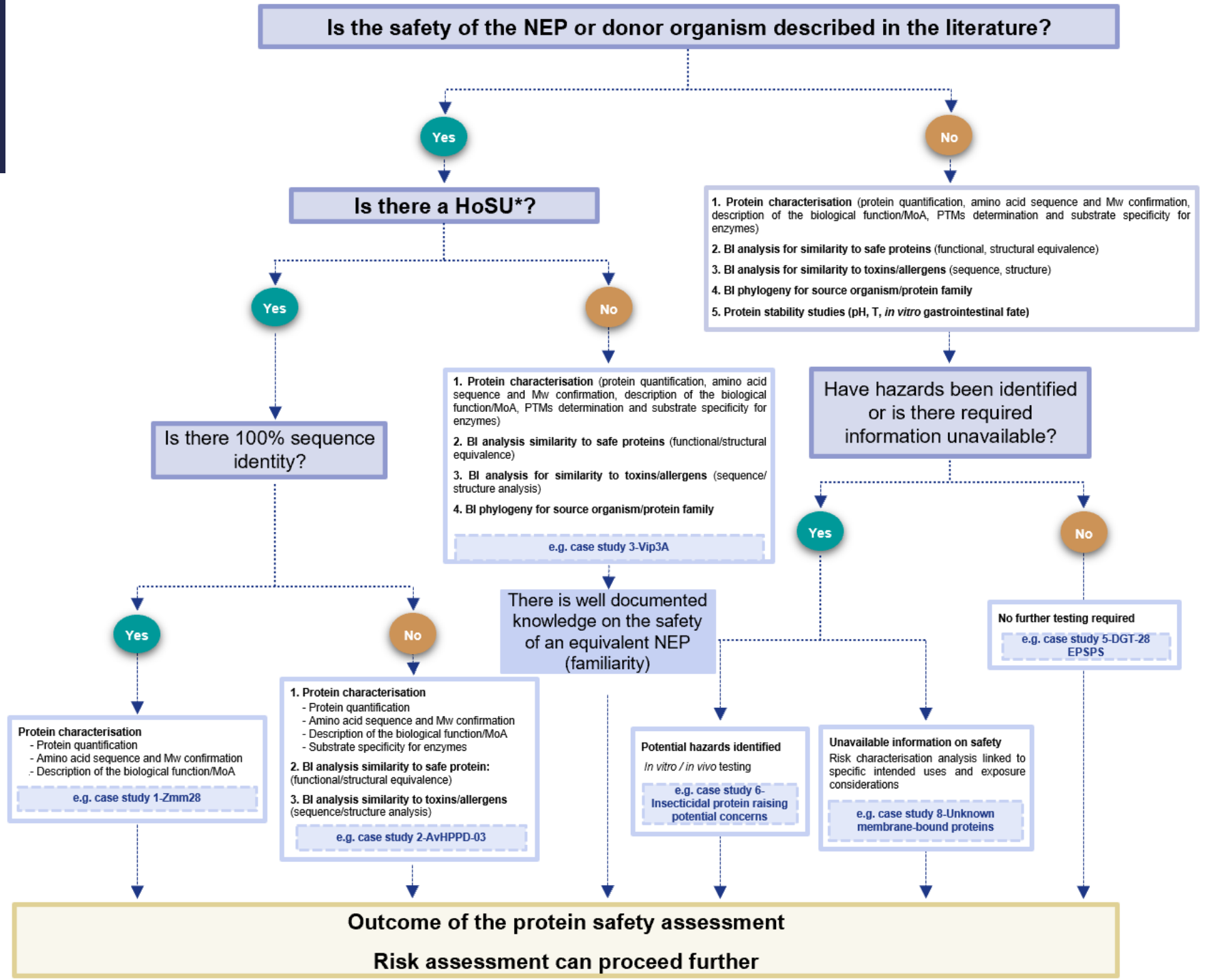
Standardisation and validation of new methods

Experimental shift within a weight-of-evidence approach

Need for complementary/alternative methods

PROTEIN SAFETY – DEVELOPMENTAL PROJECTS

- Sub-project I, Allergenicity assessment: developing novel approaches to increase reliability of predictions and to be future-ready (Published)
- Sub-project II, Enhancing the toxicological assessment of proteins in food/feed: exploring *in silico* (Published) and *in vitro* (Published) tools and novel strategies. Procurement on processing (Published)
- Sub-project III, Development of an adverse outcome pathway (AOP) for celiac disease (Published) and OECD-EFSA doc to be published in 2025
- Sub-project IV, Risk assessment methodology for Open Reading Frames in GMO applications (Published)
- Software tool to predict peptide binding to HLA-DQ2 and HLA-DQ8 – celiac disease, Published (new activities ongoing to update the tool)


Is the safety of the NEP or donor organism described in the literature?
Yes
No
Is there a HoSU*?
1. Protein characterisation (protein quantification, amino acid sequence and Mw confirmation, description of the biological function/MoA, PTMs determination and substrate specificity for enzymes)
2. BI analysis for similarity to safe proteins (functional, structural equivalence)
3. BI analysis for similarity to toxins/allergens (sequence, structure)
4. BI phylogeny for source organism/protein family
5. Protein stability studies (pH, T, in vitro gastrointestinal fate)
Yes
No
Is there 100% sequence identity?
1. Protein characterisation (protein quantification, amino acid sequence and Mw confirmation, description of the biological function/MoA, PTMs determination and substrate specificity for enzymes)
2. BI analysis similarity to safe proteins (functional/structural equivalence)
3. BI analysis for similarity to toxins/allergens (sequence/ structure analysis)
4. BI phylogeny for source organism/protein family
e.g. case study 3-Vip3A
Have hazards been identified or is there required information unavailable?
Yes
No
Yes
No
There is well documented knowledge on the safety of an equivalent NEP (familiarity)
No further testing required
e.g. case study 5-DGT-28 EPSPS
Protein characterisation
- Protein quantification
- Amino acid sequence and Mw confirmation
- Description of the biological function/MoA
e.g. case study 1-Zmm28
1. Protein characterisation
- Protein quantification
- Amino acid sequence and Mw confirmation
- Description of the biological function/MoA
- Substrate specificity for enzymes
2. BI analysis similarity to safe protein: (functional/structural equivalence)
3. BI analysis similarity to toxins/allergens (sequence/structure analysis)
e.g. case study 2-AvHPPD-03
Potential hazards identified
In vitro / in vivo testing
e.g. case study 6- Insecticidal protein raising potential concerns
Unavailable information on safety
Risk characterisation analysis linked to specific intended uses and exposure considerations
e.g. case study 8-Unknown membrane-bound proteins
Outcome of the protein safety assessment
Risk assessment can proceed further

MAIN CONCLUSIONS

- The main purpose of this document is to provide a critical evaluation of the overarching framework for protein safety assessment of NEPs
- This document is NOT intended to provide guidance on current assessment of NEPs
- But it aims to illuminate key challenges and gaps in this field, and to explore potential avenues for addressing these issues in the near to medium term
- Risk assessment strategies needs to evolve as Science and Technology does. There is a need for discussion and consensus on how new methodologies should be used in the WoE approach for NEPs and their value when integrated with current testing
- The EFSA GMO Panel is committed to reducing/replacing animal studies while consistently ensuring a high level of consumer protection. A stepwise approach is recommended, where animal studies and/or more targeted *in vitro* testing are only employed when strictly necessary
- It is timely to revisit and clarify the purpose of the protein safety risk assessment to ensure that NEPs in GMOs are evaluated in an appropriate, consistent, and proportionate manner

MANDATE TIMELINES

Survey

Open until 18th Feb 2024

Public consultation

Q1 2025

Adoption of the Scientific Opinion

Middle 2025

Time to act by all parties involved

OECD workshop & EFSA Developmental projects

THANK YOU!

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EUROPEAN FOOD SAFETY AUTHORITY

Review of risk assessment methodology for RNAi-based GM plants

18th GMO Network meeting

17/11/2024

EUROPEAN FOOD SAFETY AUTHORITY

PROJECT AIMS

EFSA's objective: in order to update EFSA's guidance documents, the scientific literature is regularly reviewed and the RA methodologies are updated to follow the progress in knowledge in the field

Literature searches to determine the need for update of EFSA's strategy for the RA of RNAi-based GM plants

Bioinformatic tool delivered by EFSA to the applicant to harmonise plant RNAi off-target searches

Guidance document on RNAi-based GM plants

EFSA GUIDANCE: RISK ASSESSMENT CONSIDERATIONS FOR RNAI-BASED GENETICALLY MODIFIED PLANTS

- Legal basis: Commission Implementing Regulation 503/2013, section 1.2.2.3 (e)
- Based on previous EFSA work: Pačes et al., 2017, Dávalos et al., 2019, Papadopoulou et al., 2020 and recent literature findings
- To supersede Annex II to the 118th GMO Panel meeting minutes
- **To be published at the beginning of 2025**

EFSA GUIDANCE: RISK ASSESSMENT CONSIDERATIONS FOR RNAI-BASED GENETICALLY MODIFIED PLANTS

Topics to be covered:

- Bioinformatic analyses: parameters for in-silico off-target searches, considerations on how results should be discussed
- Expression of the insert
- RNAi stability and effects on humans/animals
- Dietary exposure to short RNAs

BIOINFORMATIC TOOL ON FOR PLANT RNAI OFF-TARGETS

- A script to be used for the IR 503/2013-required dsRNA off-target analysis, in plants
- The analysis will not be performed in EFSA environment
- To be run by the applicants; independent of EFSA submission tools
- Outcome will not be known/stored in EFSA; is owned by the applicant
- The result to be analysed by the applicant and submitted in the respective study with the GMO application dossier
- To be made available through an open-source repository

PROJECT TIMELINE

Project start: December 2022

Literature search: June 2024

Bioinformatic tool: June 2024

Guidance document for consultation: end of 2024

Project end and guidance publication: Q1 of 2025

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