# CSO-03 – NOVEL STRATEGY FOR ALLERGENICITY RISK ASSESSMENT

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Chief Scientist Office

MOTIVATION

Allergenicity RA is a **cross-cutting** issue for EFSA Scientific Units/Panels dealing with proteins (**regulated products**)

- To keep up with the rapid pace of food **innovation**

- To ensure food is **safe** for consumption & does not contribute to the **rising burden** of food allergies
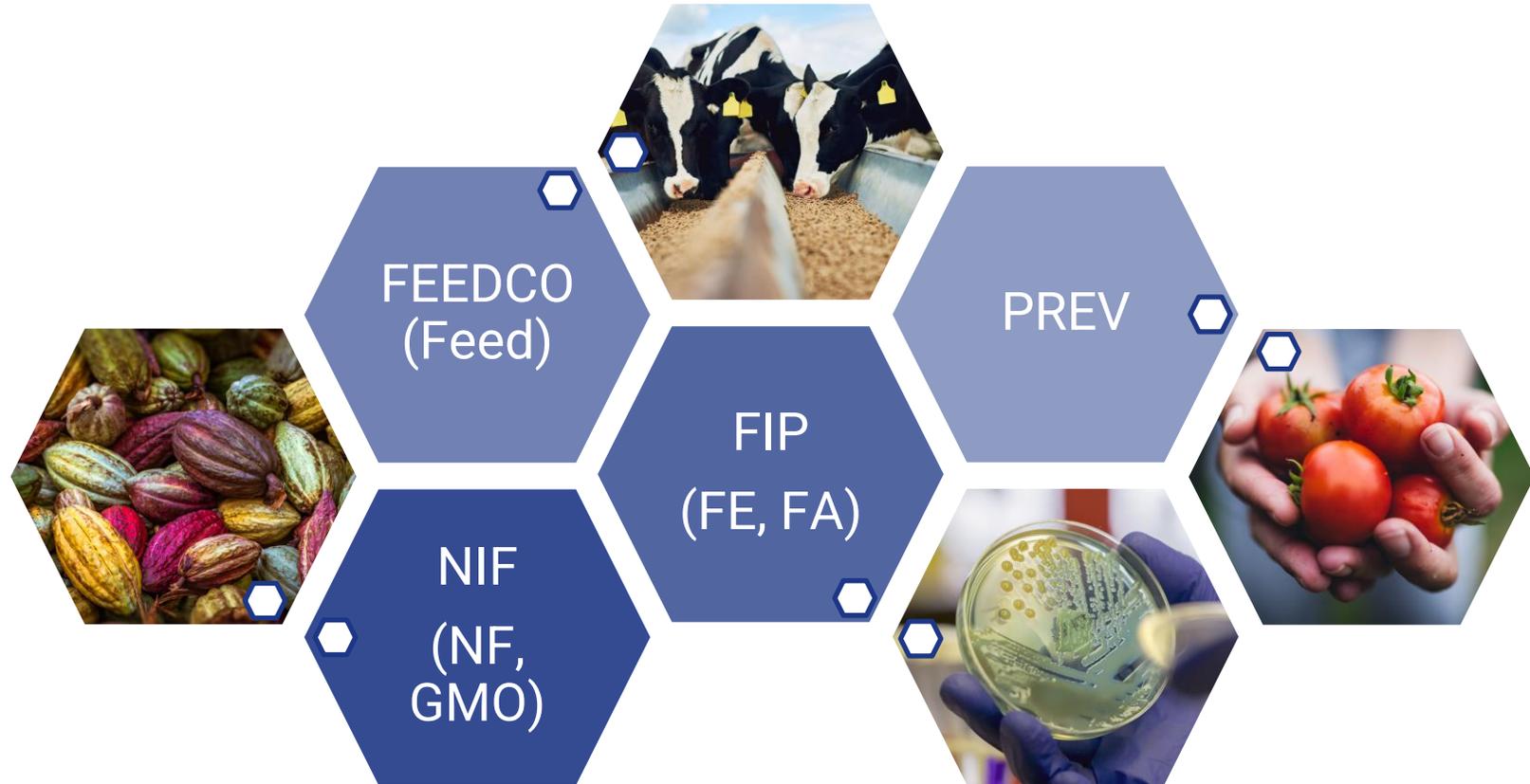
MOTIVATION

▶ Allergenicity RA is primarily informed by **2003 Codex Alimentarius guidelines** (*"foods from modern biotechnology"*)

- Focus on newly expressed proteins (**NEPs**) in GMOs
- Suggest an integrated, **stepwise**, case-by-case approach as no single test can predict allergenicity:

1. Allergenicity of protein source
⌄
2. Amino acid sequence homology
⌄
3. Resistance to pepsin digestion
⌄
4. Specific serum screening
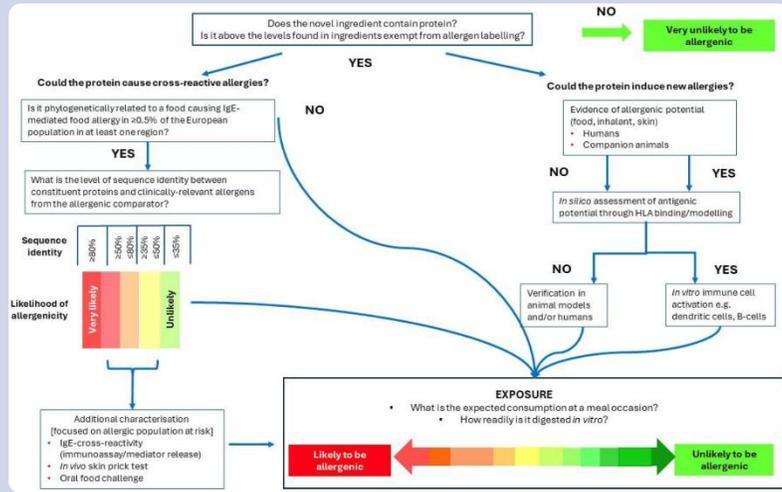⌄
5. Other considerations

While the overall tiered approach remains valid, certain methodologies would benefit from closer alignment with **state-of-the-art** scientific advances

MOTIVATION

Ranking method & screening tools for allergy RA of innovative proteins

(Mills et al., 2024)

EFSA guidance on NF

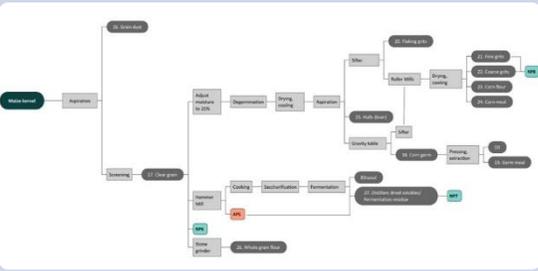(EFSA NDA Panel, 2024)
(Laganaro et al., 2025)

Allergenicity RA of innovative proteins – Training for EFSA staff

UMC Utrecht

UNIVERSITY OF SURREY

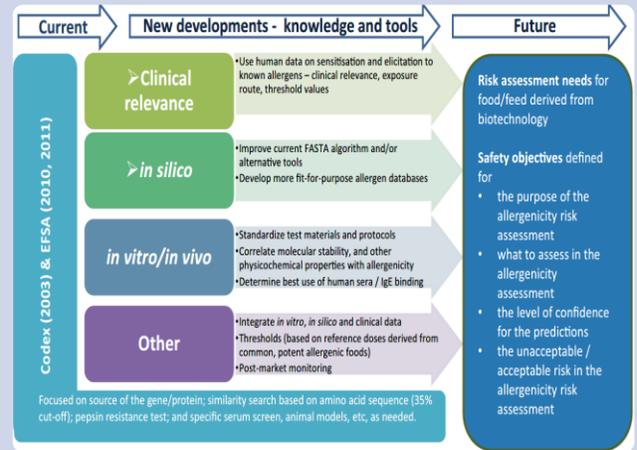(NP/EFSA/NIF/2025/01)

Effect of processing on protein safety
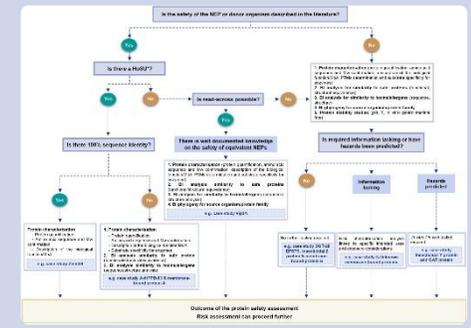

(Martinez et al., 2024)

Development needs for allergenicity & protein safety assessments

(EFSA GMO Panel, 2022)

Safety assessment of newly expressed proteins in GM plants

(EFSA GMO Panel, 2025)

MOTIVATION

		Requirements outlined in the guidance	Challenges and knowledge gaps	Future perspectives
EFSA's updated NF guidance: Allergenicity assessment tiered approach	Tier I	•Comprehensive literature review of the NF •Phylogenetic relationship of the NF with known allergenic sources	•Need for appraisal criteria for allergenicity studies •Phylogenetic similarity does not guarantee a shared immune response •Low predictive power of phylogenetic analysis for microbial novel proteins	•Ranking existing evidence according to reliability of the studies (appraisal tool). •Integration of structural similarity into phylogenetic analysis •Production of reference data for microbial novel proteins
	Tier II	•Bioinformatic search for cross-reactivity, i.e., AAS comparison and complementary approaches	•Need for *in silico* prediction tools for cross-reactivity and *de novo* sensitization considering clinical relevance •Search results vary as different search engines have different goals, type of data archived, and accessibility •Lack of internationally recognized structural features distinguishing allergens from non-allergens	•Reliable, updated and harmonized databases with ranking strategy according to clinical relevance •Predictive 3D structure analysis and machine learning based on conformational IgE epitope matching
	Tier III	•Human serum specific IgE binding assay using immunoassay methods such as ELISA or electrophoresis combined with immunoblotting with serum IgE sera	•Need for clear guidance for IgE binding tests (e.g., sera for rare allergens, individual *vs.* pooled sera, test population, and negative controls) •IgE binding assays cannot distinguish between sensitized and allergic individual	•Definition of test parameters for IgE binding assays •Assessing different endpoints of food allergy, using new methodologies like BAT and T cell assays once validated
	Tier IV	•Human studies, e.g. SPT or OFC (preferably DBPCFC) in subjects with confirmed food allergy to the known allergen	•Need for standardisation of testing conditions for SPT •OFC are time-consuming and resource-intensive	•Development of standardised guidelines for *in vivo* assays •Validation and implementation of animal studies

Need for defined criteria/scenarios that trigger each tier and thresholds of allergological concern

MOTIVATION

New editorial | EFSA's Research & Innovation Needs

CSO

Published 05/05/2025 · 1 min read

A new editorial has been published, highlighting key research and innovation (R&I) needs to support EFSA's regulatory science. The focus areas include:

- Omics technologies
- Gut microbiome
- New approach methodologies (NAMs)
- Allergenicity risk assessment
- Aggregate exposure assessment
- Environmental risk assessment (ERA)

The document highlights emerging challenges and opportunities, calls for transdisciplinary research, and emphasizes the interconnectedness of human, animal, plant, and environmental health.

This resource is valuable for stakeholders and funders in shaping future research and funding initiatives related to food safety.

"This editorial highlights key research and innovation needs to support future regulatory sciences linked to food safety, spanning omics, the gut microbiome, NAMs, allergenicity, exposure, and environmental risk assessment

Carlos das Neves
Chief Scientist
EFSA

efsa

Advancing EFSA's regulatory science: Updated research and...

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MOTIVATION

Call for revision of allergenicity RA methodologies to remain F4P and better inform decision-making

EFSA'S STRATEGIC PRIORITIES
(EFSA Strategy 2027)

EOR 1.1.1 — ↑ Quality and efficiency of RA (regulated products)

EOR 2.1.3 — ↑ Capacity for future RA challenges

Call for revision of allergenicity RA methodologies to remain **F4P** and better inform decision-making

EFSA Scientific Opinions on the safety of **insects** as **Novel Foods**

EFSA NDA Panel: "*Research* to be undertaken on *allergenicity* of insects, including *cross-reactivity*"

Ongoing dialogue with **DG SANTE** on allergenicity of innovative proteins

OBJECTIVES

O1. Open-source *in silico* prediction/ appraisal tool for clinical cross-reactivity

▶ Curated allergen **database** ranked according to **clinical relevance**

▶ **Integrated** phylogenetics, sequence homology and structural similarity

O2. Open-source *in silico* prediction/ appraisal tool for *de novo* sensitisation

▶ Modelling of protein **binding** capacity to antigen-presenting cells (HLA)

▶ Other aspects informing on sensitisation capacity (e.g., **molecular patterns**)

Novel strategy for F4P allergenicity RA

• **Reliability** & **speed of RA**

• **Simplification** & **harmonisation**

Better-informed decision-making

O3. Verification of *in silico* predictions and future prospects of *in silico* tools

▶ Generation of **experimental** *in vitro* and *in vivo* (human or animal) data

▶ **Impact** of protein digestibility, food matrix and processing on protein properties & allergenic potential

O4. Novel strategy for allergenicity RA

▶ **Thresholds** of allergological concern

▶ **Systematic tiered approach**:
  • Clinically-relevant cross-reactivity
  • *De novo* sensitisation
  • Decision-making framework (criteria for each tier)

IRMA
Innovative Risk Assessment
Methodologies Programme

PROJECT TIMELINE

EXPECTED CALL LAUNCH
March 2026

PIN ON EU FUNDING &
TENDERS PORTAL

**SINGLE FRAMEWORK CONTRACT
(€1.3 M)**

2026		**2027**				**2028**				**2029**				**2030**		
Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3

SC1 – €160k (6 m)

Inception report

Literature review on **future prospects** for *in silico* prediction tools

SC2 – €430k (16 m)

Allergen **database** (**clinical relevance**)

Mathematical **models for *de novo* sensitisation** potential

Experimental *in vitro/in vivo* testing

SC3 – €430k (16 m)

In silico prediction/appraisal **tool for clinical cross-reactivity**

In silico prediction/appraisal **tool for *de novo* sensitisation**

Experimental *in vitro/in vivo* testing

SC4 – €280k (10 m)

Thresholds of allergo-logical concern

Systematic tiered approach (decision-making framework)

EFSA RESOURCES

PROJECT STEERING COMMITTEE

- Ana Afonso (Project Owner)
- Claudia Heppner (Solution Provider)
- Claudia Paoletti (IRMA Programme Manager)
- Ioannis Marios Sarikas (IRMA Programme Officer)
- Estefanía Noriega Fernández (Business Manager)

INVOLVED UNITS

- NIF (Novel Foods, GMO)
- FIP (Food enzymes, Food Additives)
- FEEDCO (Feed additives)
- PREV
- KNOW
- IDATA
- CSO

CONTRIBUTORS

- Alejandra Muñoz González (ISA expert)
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