PARMA SUMMER SCHOOL

26 – 28 SEPTEMBER 2023

Innovative food products

Allergenicity of novel foods – The case of insects

Cristiano Garino, German Federal Institute for Risk Assessment (BfR), Dept. Food Safety, Berlin, Germany

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Agenda

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- Novel food allergy
- Approaches to allergenicity risk assessment: the ImpARAS COST action
- EFSA Scientific Opinion on allergenicity and protein safety assessment of food and feeds derived from biotechnology
- Insects as novel food allergens

What is food allergy?

Adverse reaction to an otherwise harmless food or food component that involves an abnormal response of the body's **immune system** to specific **proteins** in foods''

(FAO and WHO, 2001)

Why is important to study it?

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High prevalence: point prevalence of self-reported FA in Europe is 13.1% (95% CI 11.3–14.8) *Spolidoro et al., Allergy, 2022*

Symptoms of an allergic reaction may involve the skin (rushes, hives, pale or blue coloring), the oral and gastrointestinal tract (swelling of the tongue, tight or hoarse throat, trouble swallowing, vomiting and/or stomach cramps, diarrhea), the respiratory tract (shortness of breath, wheezing, repetitive cough) and the cardiovascular system (weak pulse, dizziness or feeling faint, anaphylactic shock or circulatory collapse).

Social and economical impact

Causes unclear, no cure

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What is the mechanism?

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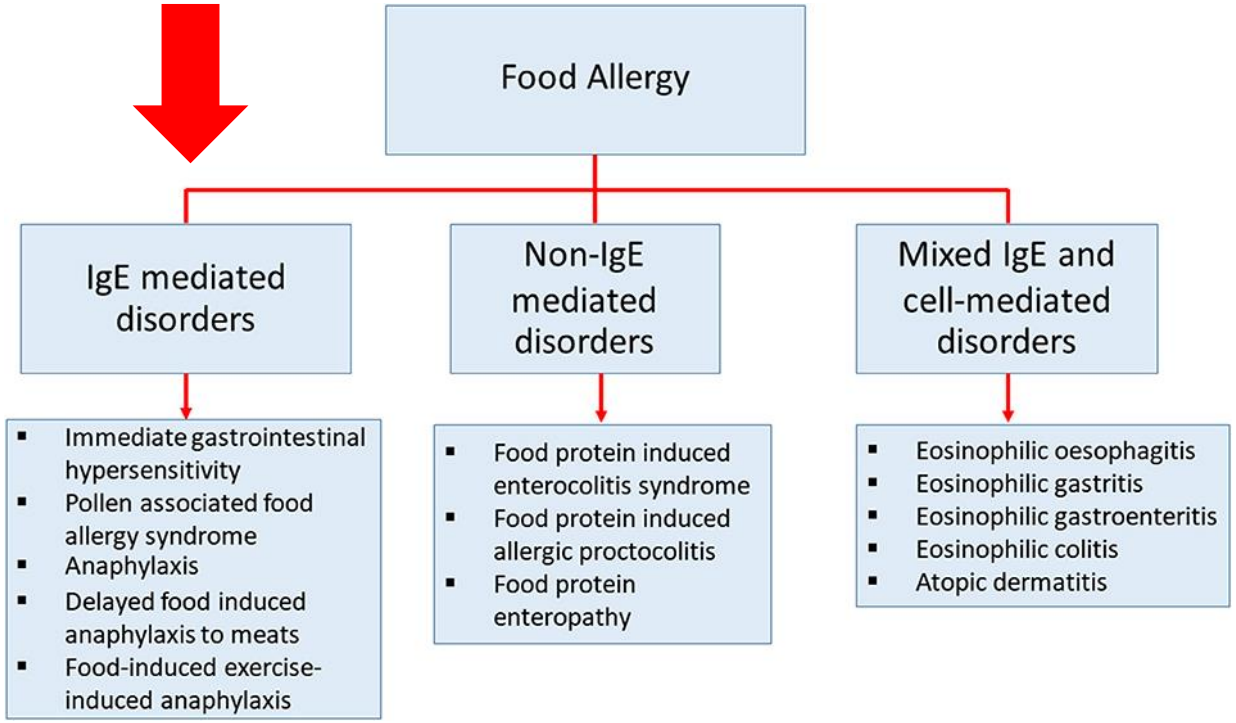
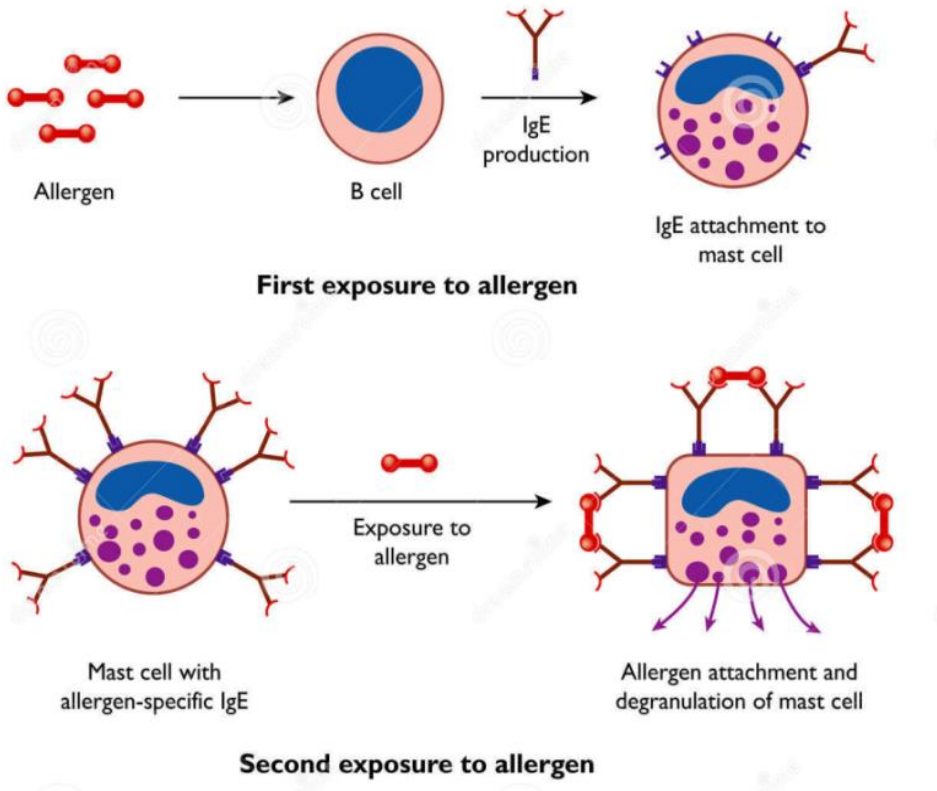


Satitsuksanoa et al., Sec. Immunological Tolerance and Regulation, 2018



Dijk et al., Compr. Rev. Food Sci. Food Saf., 2023

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Novel food allergens

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Allergology International
Volume 72, Issue 2, April 2023, Pages 279-285

Original Article

Nattokinase (Bac s 1), a subtilisin family serine protease, is a novel allergen contained in the traditional Japanese fermented food natto

Kayoko Suzuki [a], Masashi Nakamura [b c], Nayu Sato [b c], Kyoko Futamura [a], Kayoko Matsunaga [a b], Akiko Yagami [a]

Food Chemistry
Volume 395, 30 November 2022, 133586

Novel alimentary pasta made of chickpeas has an important allergenic content that is altered by boiling in a different manner than chickpea seeds

Rafael Valdelvira, Guadalupe Garcia-Medina, Jesus F. Crespo, Beatriz Cabanillas

Original Paper | Published: 03 August 2022

Allergenic Content of New Alimentary Pasta Made of Lentils Compared with Lentil Seeds and Analysis of the Impact of Boiling Processing

Rafael Valdelvira, Guadalupe Garcia-Medina, Jesus F. Crespo & Beatriz Cabanillas

Plant Foods for Human Nutrition **77**, 443–446 (2022) | Cite this article

Journal of Applied Phycology
https://doi.org/10.1007/s10811-022-02880-2

Edible algae allergenicity – a short report

Christopher A. James[1,2] · Simon Welham[1] · Peter Rose[1]

PAI PEDIATRIC ALLERGY AND IMMUNOLOGY
EAACI

ORIGINAL ARTICLE | Open Access

Allergenic risk assessment of cowpea and its cross-reactivity with pea and peanut

Mouhamed Mounir Chentouh, Françoise Codreanu-Morel, Aissa Boutebba, Stephanie Kler, Dominique Revets, Annette Kuehn, Markus Ollert, Christiane Hilger

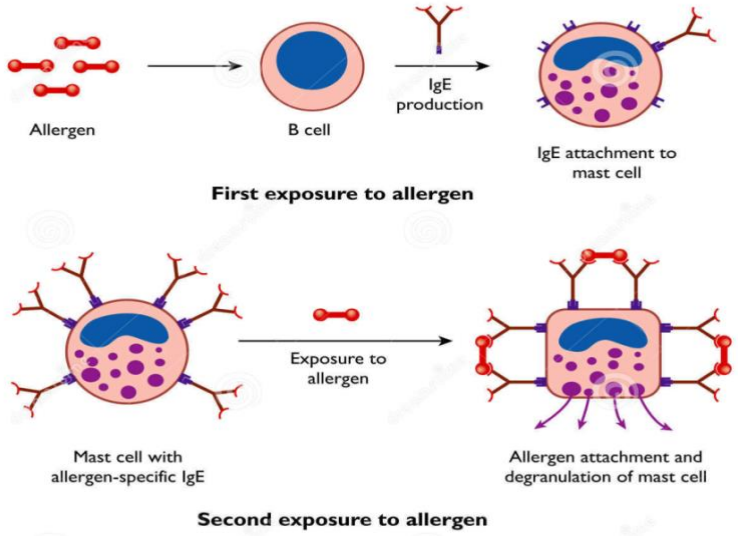
Open Access

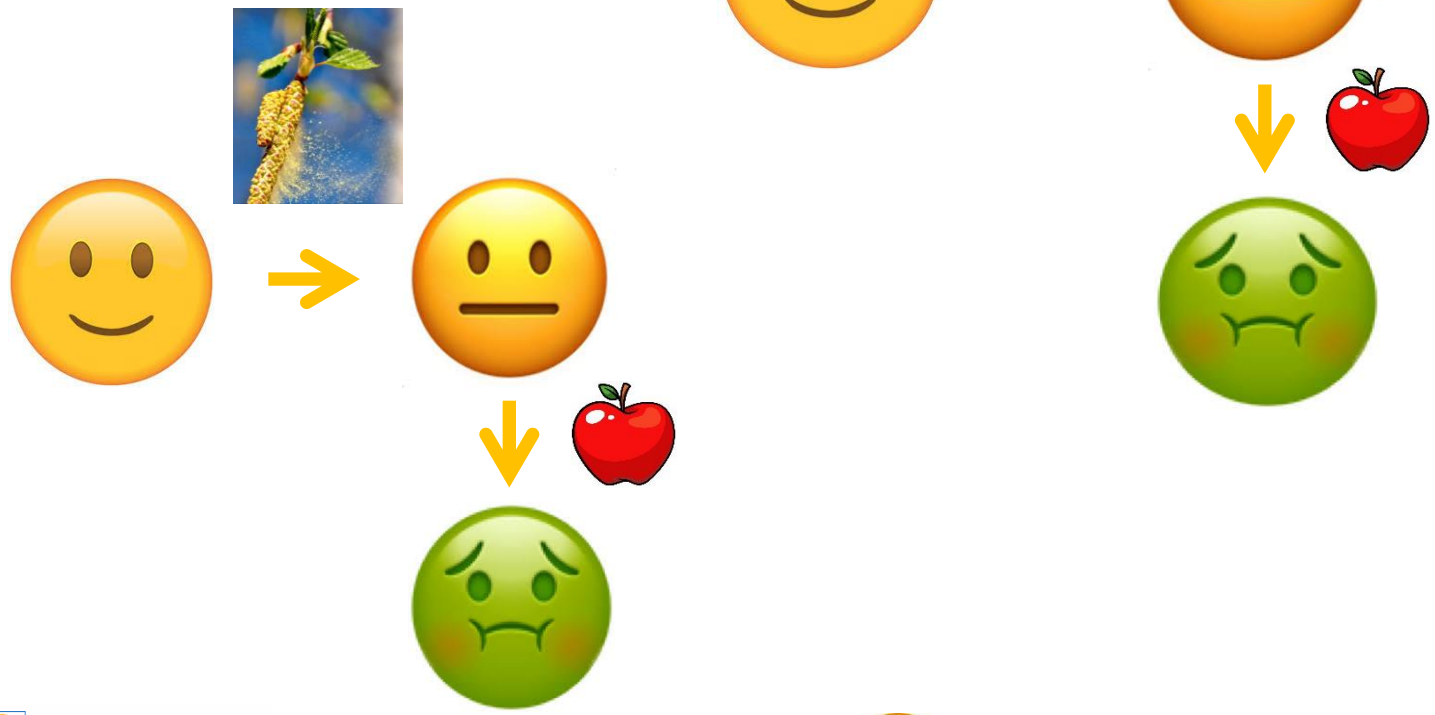
Veganism and food allergies - when the exclusion of animal products and allergens coincide

Lindsay Archibald-Durham[0]
Affiliations

Published Online: 1 Jun 2021 • https://hdl.handle.net/10520/ejc-caci-v34-n2-a5

Primary sensitization *vs* cross-reactivity





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EFSA Guidance on applications for novel foods, 2021

The default assumption for novel foods containing proteins is that they have allergenic potential.

A comprehensive literature review is needed in order to retrieve available information on sensitization, case reports of allergic reactions, and/or allergenicity studies (*in vitro*, in animals, in humans) of the novel food and/or its source(s)

Appropriate methods to further investigate the potential allergenicity:

Protein analysis

- Protein content in the novel food
- Molecular weight of the potentially allergenic protein, heat stability, sensitivity to pH, digestibility by gastrointestinal proteases
- Degree of sequence homology with known allergens
- Immunological tests (e.g. western blotting)

Human testing

- Detection of specific IgE antibodies
- Skin prick testing
- Double-blind placebo-controlled food challenge studies.

EFSA NDA Panel, Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes, 2014. Codex Alimentarius, 2003–2009. Foods derived from modern biotechnology.

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Home > Browse Actions > Improving Allergy Risk Assessment Strategy for new food proteins (ImpARAS)

Description | Parties | Management Structure

Description

Due to the continuing growth of the world population from 7 billion today to 9 billion in 2050, we will face a shortage of protein sources for human consumption in the near future. For this reason, Horizon 2020 included the topic: "*Sustainable European bio-economy; bridging the gap between new technologies and their implementation*" within their research program. Food safety assessment is an important requirement before new products can be brought to market. Such assessments include the investigation of microbiological and toxicological hazards as well as the risk of food allergy.
From an industry perspective, there is a need for a) relatively cheap, easy and reliable tools for screening for allergenicity of new or modified food proteins, b) early risk based decision-making during product development and c) an improved risk assessment strategy accepted by regulatory authorities.
The new multi-disciplinary scientific network will improve strategies to predict the allergenicity of novel or modified proteins or proteins from novel sources with novel and innovative approaches that have not previously been identified. This will allow the transfer of scientific advances to European food companies to develop safe products, advise food safety authorities on better risk assessment strategies and change public opinion on the safety of novel sustainable food.

Action Details

MoU - 034/14
CSO Approval date - 14/05/2014
Start date - 08/12/2014
End date - 08/12/2018
http://www.imparas.eu

This Action has ended

- Read the Project Description MoU

www.cost.eu/actions/FA1402/

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Verhoeckx *et al. Clin Transl Allergy* (2020) 10:13
https://doi.org/10.1186/s13601-020-00318-x

Clinical and Translational Allergy

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REVIEW Open Access

COST Action 'ImpARAS': what have we learnt to improve food allergy risk assessment. A summary of a 4 year networking consortium

Kitty Verhoeckx[1*], Katrine Lindholm Bøgh[2], Anne Constable[3], Michelle M. Epstein[4], Karin Hoffmann Sommergruber[5], Thomas Holzhauser[6], Geert Houben[1], Annette Kuehn[7], Erwin Roggen[8], Liam O'Mahony[9], Ben Remington[1] and René Crevel[10]

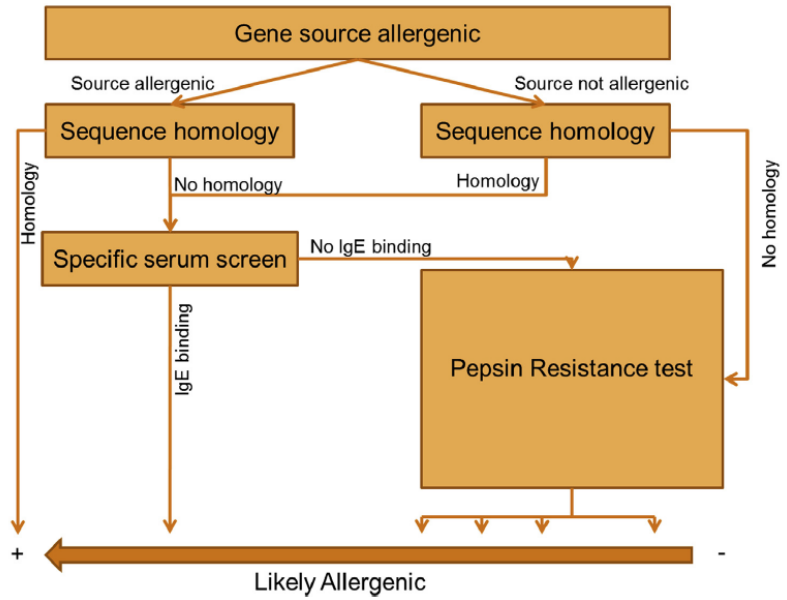

Fig. 1. Flow chart summarizing the Weight-of-evidence approach for allergenicity assessment of newly expressed proteins in GMO.

Verhoeckx et al., Reg. Toxicol. Pharmacol. 2016

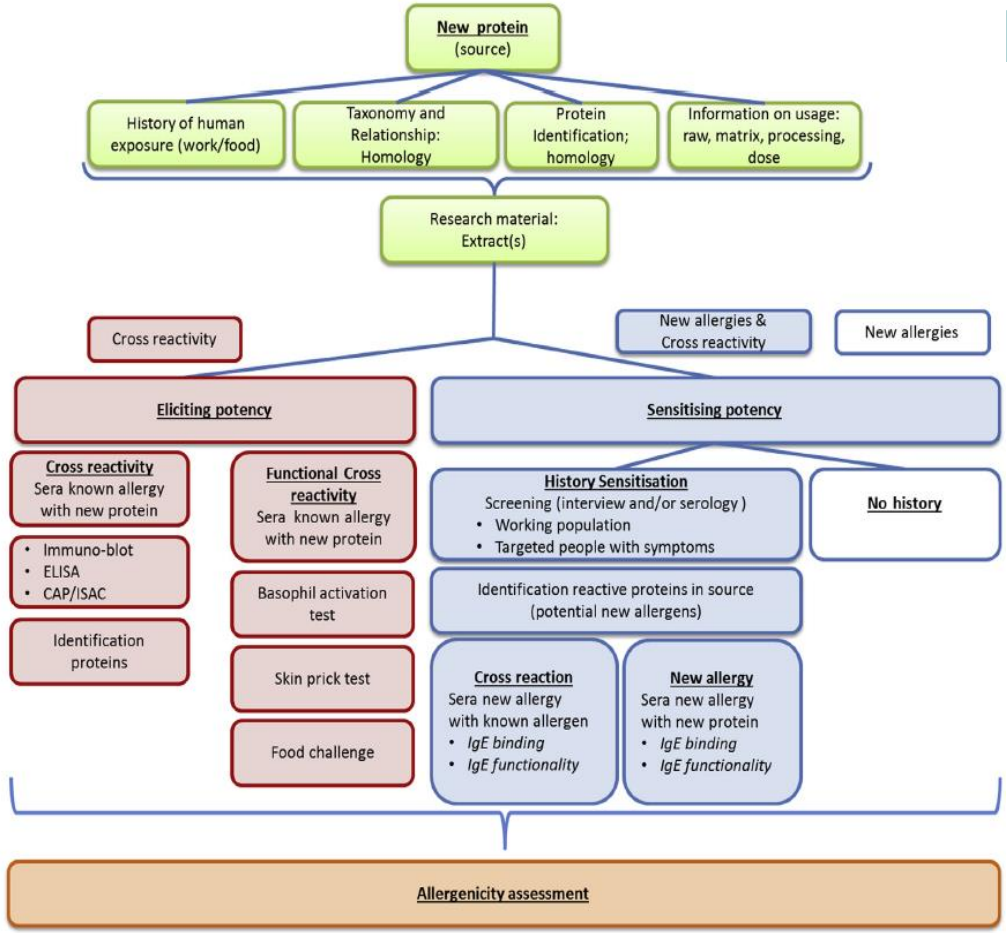

Fig. 2. Schematic overview of suggested allergenicity assessment strategy of novel proteins and protein containing sources.

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REVIEW
Food Allergies

Molecular Nutrition & Food Research
www.mnf-journal.com

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Current (Food) Allergenic Risk Assessment: Is It Fit for Novel Foods? Status Quo and Identification of Gaps

*Gabriel Mazzucchelli, Thomas Holzhauser, Tanja Cirkovic Velickovic, Araceli Diaz-Perales, Elena Molina, Paola Roncada, Pedro Rodrigues, Kitty Verhoeckx, and Karin Hoffmann-Sommergruber**

WG1: physicochemical properties of proteins impacting allergenicity

Methods and tools	Features and limitations	Recommendations for further research
Allergen databases	Different databases provide different levels of information; Some of them are not regularly updated/curated and therefore relevant information is missing or available information outdated; Inclusion criteria for allergenic proteins vary for individual databases	Linking of existing (allergen) databases; Harmonisation of inclusion criteria for allergens; Experimental studies in B- and T cell epitopes and implications on cross- reactivity; Improving predictive algorithms for sensitising potential of proteins linked with and without clinical relevance;
Analytical methods	Highly sensitive and advanced methods available for protein characterisation; Sample preparation especially for complex food extracts is sometimes difficult (lack of harmonised protocols);	Harmonisation of method protocols; Improvements in sample preparation; Generation of scientific evidence of certain structural determinants (glycosylation, aggregation etc.) linked with increased allergenicity, which is currently lacking;
IgE binding assays	Well standardised reference assays including reference proteins are missing. In case of novel proteins, no reference material is available; If sIgE is not available, animal-derived antibodies can be used;	Identification and generation of suitable reference proteins;
Digestion assays	Different protocols for protein digestion are available; However, harmonised protocols are needed; Lack of guidance how to interpret data, and lack of reference material; Evidence of linking protein stability and de novo sensitisation is missing;	Development of reference materials and harmonised protocols; Performance of harmonised digestion assays in ring trials with reference materials; Animal studies on comparative digestion and de novo sensitisation;
Food processing techniques	Knowledge on food processing and its impact on allergenicity is incomplete on a qualitative and quantitative level. Limited knowledge about the most effective methods (combinations), including novel processing techniques;	More data on processed food proteins and their allergenicity required; To identify the most important (combination of) processing techniques with an impact on allergenicity;
Food matrix	Analytical methods are established—but limited data are available showing a link of food matrix components to allergenicity; Limited knowledge available about food components and their interaction with allergens;	Studies required on food matrix composition and interaction with individual food proteins in model systems; Identification of relevant immunomodulating food matrix components;
Biological assays	Cellular and animal models are established but reliable assays for detection of de novo sensitisation are lacking	Method development to assess protein ligand binding and impact on innate and adaptive immune responses; Identification of biomarkers for de novo sensitisation

EUROPEAN

AOP of allergic sensitization

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van Bilsen *et al. Clin Transl Allergy (2017) 7:13*
DOI 10.1186/s13601-017-0152-0

Clinical and Translational Allergy

REVIEW Open Access

Application of the adverse outcome pathway (AOP) concept to structure the available in vivo and in vitro mechanistic data for allergic sensitization to food proteins

Jolanda H. M. van Bilsen[1*], Edyta Sienkiewicz-Szłapka[2], Daniel Lozano-Ojalvo[3], Linette E. M. Willemsen[4], Celia M. Antunes[5], Elena Molina[3], Joost J. Smit[4], Barbara Wróblewska[6], Harry J. Wichers[7], Edward F. Knol[8], Gregory S. Ladics[9], Raymond H. H. Pieters[4], Sandra Denery-Papini[10], Yvonne M. Vissers[11], Simona L. Bavaro[12], Colette Larré[10], Kitty C. M. Verhoeckx[1] and Erwin L. Roggen[13]

WG2

***In vitro* methods to predict sensitisation**

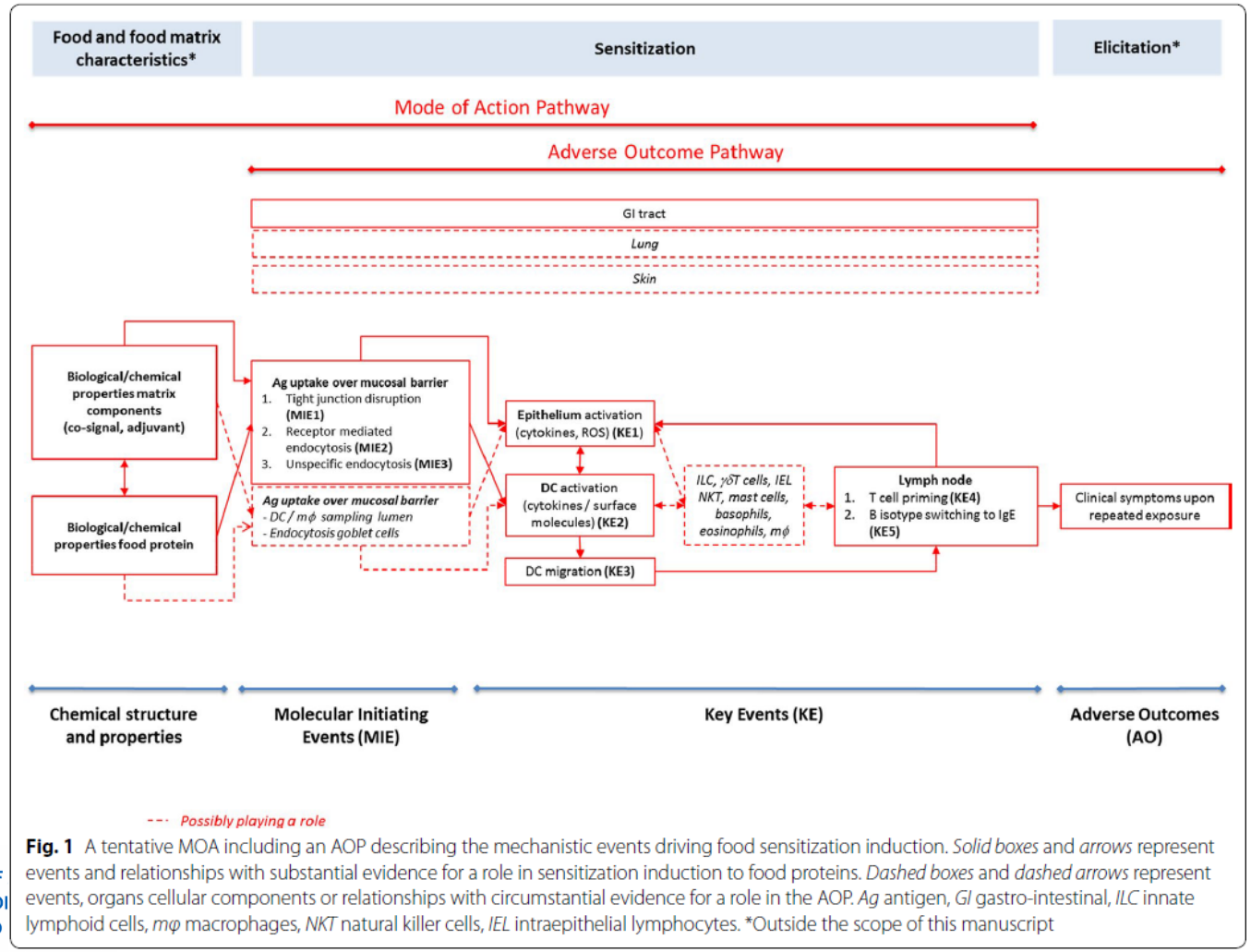

Fig. 1 A tentative MOA including an AOP describing the mechanistic events driving food sensitization induction. *Solid boxes* and *arrows* represent events and relationships with substantial evidence for a role in sensitization induction to food proteins. *Dashed boxes* and *dashed arrows* represent events, organs cellular components or relationships with circumstantial evidence for a role in the AOP. *Ag* antigen, *GI* gastro-intestinal, *ILC* innate lymphoid cells, *mϕ* macrophages, *NKT* natural killer cells, *IEL* intraepithelial lymphocytes. *Outside the scope of this manuscript

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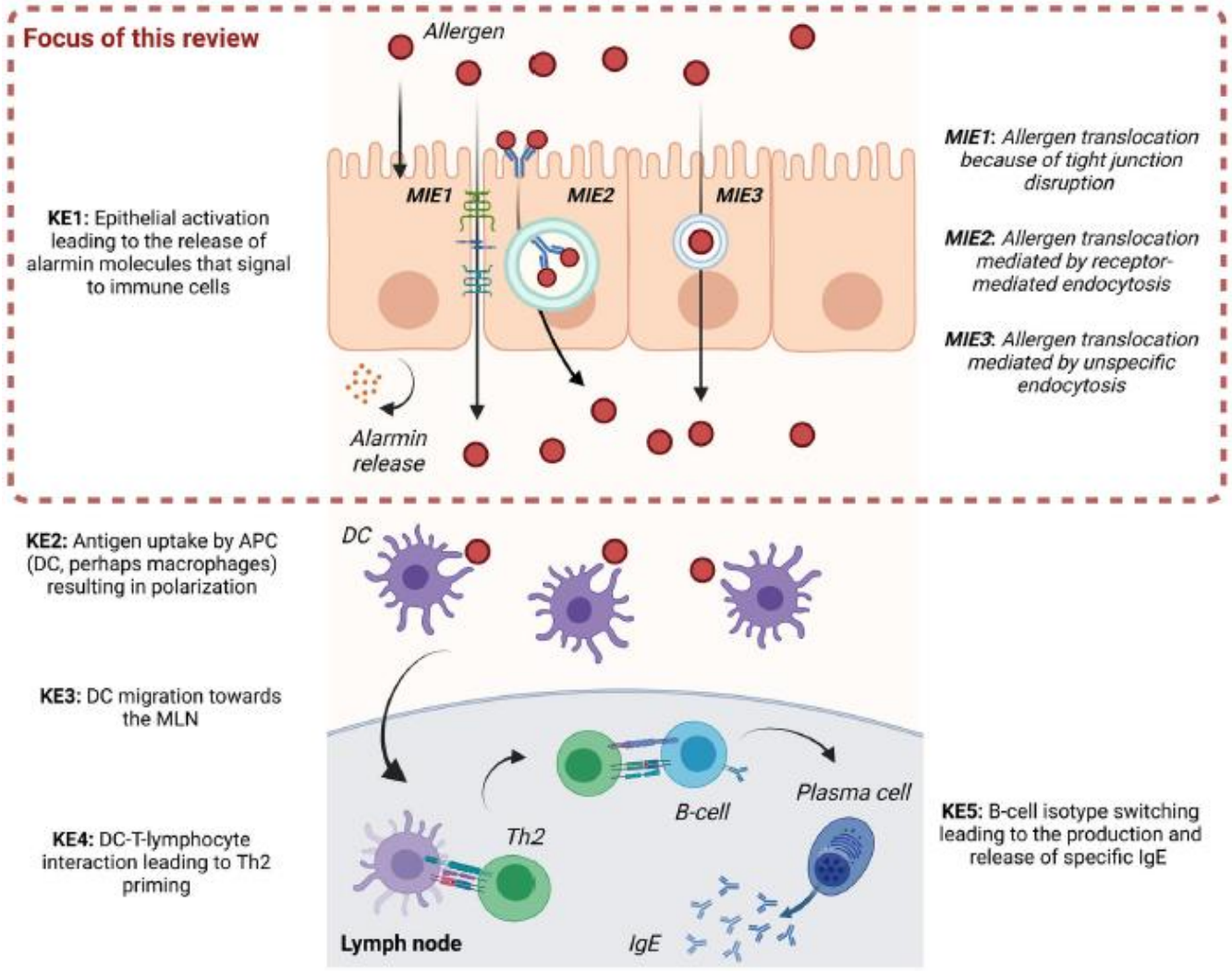
AOP of allergic sensitization



Dijk et al., Compr. Rev. Food Sci. Food Saf. 2023

WG4: Risk assessment and dissemination

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Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Defining the targets for the assessment of IgE-mediated allergenicity of new or modified food proteins

Geert Houben[a,*], Marty Blom[a], Paula Alvito[b], Ricardo Assunção[b], René Crevel[c], Christiane Kruse Fæste[d], Thuy-My Le[e], Charlotte Bernhard Madsen[f], Ben Remington[a], Thomas Stroheker[g], Emilia Vassilopoulou[h], Kitty Verhoeckx[a], Jana Žiarovská[i], Anne Constable[g]

Development of hazard and risk assessment methods have to be attuned to deliver relevant information to the risk management goal or decision to be made

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Activity 2: defining the targets for ARA

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What risk do we want to prevent?

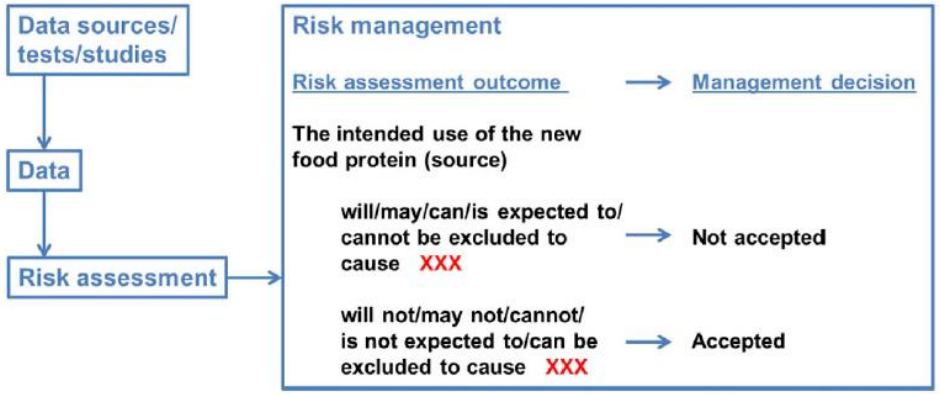

Fig. 2. The risks analysis process organized around the key parameter(s) and criterion (or criteria) for risk management decision-making.

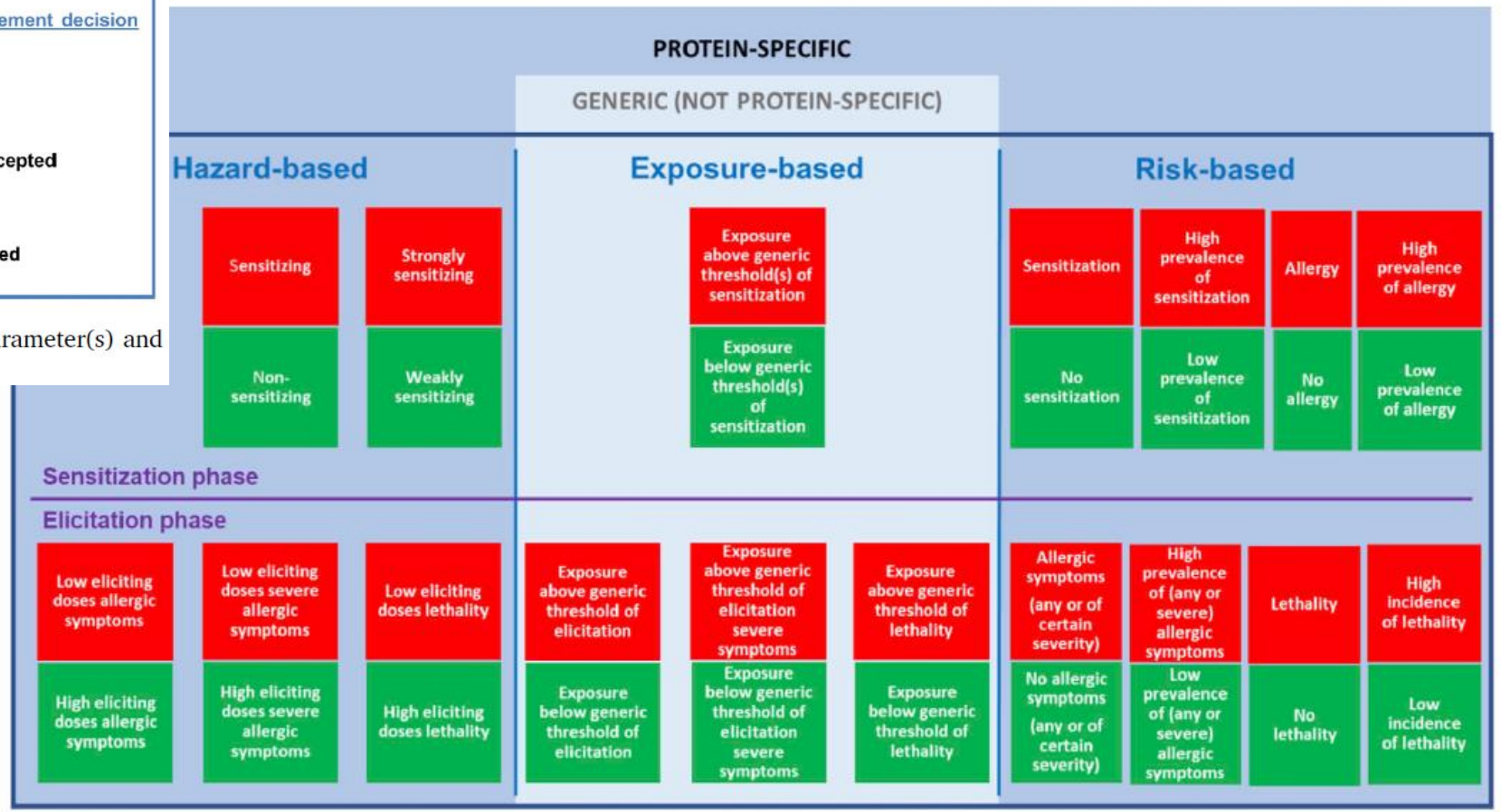

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Fig. 3. Overview of (theoretically) possible parameters (red and green boxes read horizontally across) and criteria (red versus green box) for risk management decision-making with respect to IgE-mediated allergenicity of new or modified food proteins. Risk management decision-making could be based on a single parameter/criterion or on combinations of parameters/criteria. Green: an acceptable situation; red: a non-acceptable situation. Each (theoretically) possible option has specific implications for risk management and the methods and data needed for the assessment, which are addressed in Table 1.

ImpARAS main conclusions and perspectives

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1. A **network of expertise** covering core aspects of immunology, food allergy, protein chemistry, bioinformatics, proteomics and risk modelling is needed to enable and support integrated risk assessment models and strategies.
2. A **clear outline of preferred decision-making criteria** is needed from the **risk management** sector to help researchers during method development and ensure the applicability of newly developed methods to the risk management questions at hand.
3. An agreement/consensus on a comprehensive, systematic testing and **assessment strategy** is needed to identify and characterise the risk of ***de novo* sensitisation** and allergic reactions to novel food proteins.
4. In vitro methods should focus on the different events of the **AOP** for food allergy sensitization.
5. In vitro and in vivo methods need to be harmonised and validated for instance in ring trials using specified **reference proteins/extracts**.
6. We should investigate responses to homologous series of proteins with different allergenicity, using as a starting point the ImpARAS work on **protein pairs**, in order to address the current lack of systematic data to rank existing, known allergenic proteins according to their allergenic potency.
7. Since no single distinct molecular parameter (or pattern) within one protein family seems to be exclusively responsible for the allergenic potential at the site of elicitation, a more detailed characterisation of allergens may further elucidate molecular pattern.
8. The knowledge on the impact of different **food matrices** and **food processing** on allergenicity of dietary proteins must be improved.

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SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 2 December 2021

doi: 10.2903/j.efsa.2022.7044

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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),
Ewen Mullins, Jean-Louis Bresson, Tamas Dalmay, Ian Crawford Dewhurst,
Michelle M Epstein, Leslie George Firbank, Philippe Guerche, Jan Hejatko, Hanspeter Naegeli,
Fabien Nogué, Nils Rostoks, Jose Juan Sánchez Serrano, Giovanni Savoini, Eve Veromann,
Fabio Veronesi, Antonio Fernandez Dumont and Francisco Javier Moreno

pursued further. This Scientific Opinion aims to: (i) define knowledge gaps on allergenicity prediction; (ii) identify specific research needs for improving the allergenicity risk assessment for products derived from biotechnology; (iii) determine how new basic research findings and technological developments can improve the current risk assessment methodology; and (iv) prioritise basic research funding.

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Highlights from the Summary

it is unrealistic that a single test in the short/medium term will be predictive of the allergenic potential of a protein. Therefore, the 'weight-of-evidence' approach for allergenicity assessment remains valid.

A draft of a roadmap that (re)defines the allergenicity safety objectives and risk assessment needs will be needed to address the key questions for risk assessors and risk managers, such as:

1. *what is the purpose of the allergenicity risk assessment?*
2. *what should be assessed in the allergenicity assessment?*
3. *what level of confidence is necessary for the predictions?*
4. *what is an unacceptable/acceptable risk in the allergenicity risk assessment?*

Clinical relevance

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The characterisation of an allergen involves from the analysis of its IgE antibody binding capacity to the demonstration of clinical relevance. An allergen becomes clinically relevant when it causes **symptoms** and is corroborated by **medical history** and/or provocation testing (Worm et al., 2021). The clinical relevance of individual food allergens should be a **key driver** for developing new strategies and tools for allergenicity risk assessment (EFSA, 2021). To achieve this goal, it is necessary to rely on **clinical data** of good quality and to determine criteria for describing the allergenicity of single proteins.

Although **sensitisation** is a predisposing risk factor for IgE-mediated food allergy, neither a quantitative positive specific IgE test result nor a positive skin prick test can prove the clinical relevance of a food extract or purified molecule. The ultimate means of determining the clinical relevance of an allergen molecule would be to perform a **provocation test** with a purified allergen molecule.

The clinical relevance of allergens could include criteria such as (i) the **severity** (i.e. the proportion of severe objective allergic symptoms to the potential allergen); (ii) the **potency** (i.e. the amount of the potential allergen required to cause objective symptoms); (iii) the **prevalence** of immune-mediated hypersensitivity to the potential allergen source; and iv) the **exposure route** that the allergen presents to the immune system and the **level of exposure**.

The definition of a set of **non/low-allergenic (control) proteins** is needed.

Determinants of food protein allergenicity

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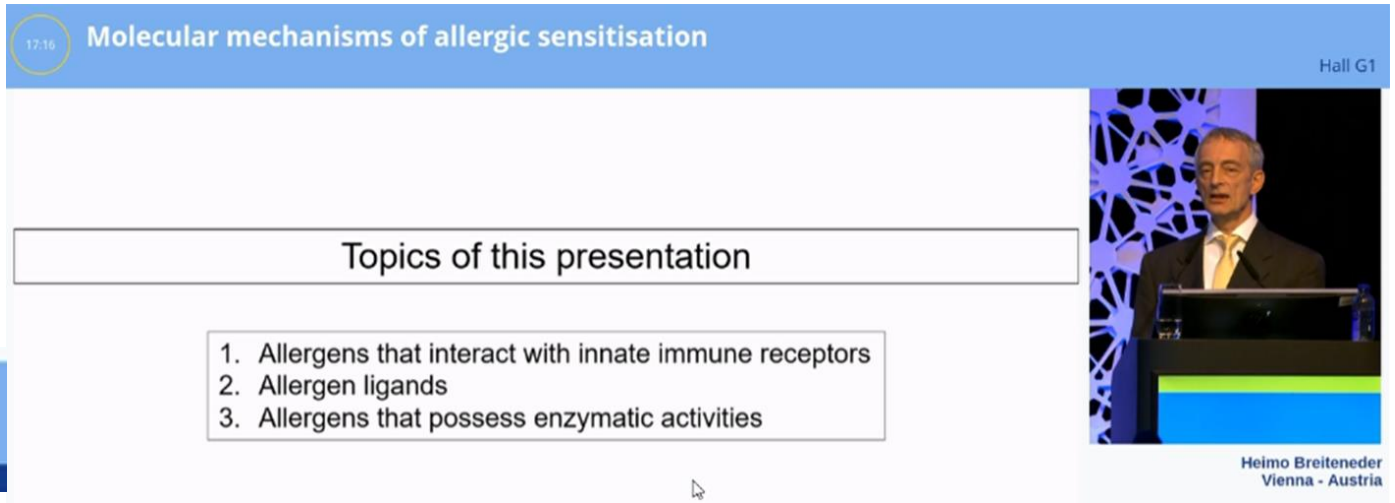
The underlying reasons why proteins or peptides become allergenic in susceptible individuals is not fully understood.

Food and pollen allergens belong to a limited number of protein superfamilies […] there are **no single common structural causes**, features or sequence motifs identified that contribute to their overall allergenicity.

Ligand-binding allergens expose the immune system to a variety of **biologically active small molecules** that could play important and still not well-understood roles in the sensitisation process in addition to the allergenic protein itself (Chruszcz et al., 2021).



Risk assessment tools for allergenicity prediction: *in silico* tools

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The *in silico* approaches are used as a first step in identifying relevant identity between a newly expressed protein and a known allergen before other confirmatory but more laborious testing are required, such as in vitro and/or in vivo studies. If **relevant shared sequence identity** is observed with a known allergen, **subsequent serum IgE binding studies** using sera from individuals with a specific, relevant type of allergy would likely follow. The **absence of sequence homology** indicates that a newly expressed protein is **unlikely to be cross-reactive** with IgE directed towards known allergens. However, current *in silico* tools used in the allergenicity assessment **does not provide information on the capacity of proteins for *de novo* sensitisation**.

ELSEVIER

Contents lists available at ScienceDirect

Regulatory Toxicology and Pharmacology

journal homepage: www.elsevier.com/locate/yrtph

Allergenicity prediction of novel and modified proteins: Not a mission impossible! Development of a Random Forest allergenicity prediction model

Joost Westerhout[a,*], Tanja Krone[a], Almar Snippe[a], Lilia Babé[b], Scott USRE. McClain[c], Gregory S. Ladics[d], Geert GF. Houben[a], Kitty CM. Verhoeckx[a]

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Risk assessment tools for allergenicity prediction: *in vitro* tools
Protein digestibility

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Factors such as food **processing, digestion, and transport** (including internal processing and presentation to the immune cells) should be ideally included in an allergenicity assessment assay; however, it is crucial to consider the feasibility and practicality of including these factors.
The **pepsin resistance test** is still performed regularly, although several studies have demonstrated that there is a **poor correlation** between resistance to pepsin digestion and allergenicity! The evidence supporting the resistance to degradation by pepsin as a direct predictor of allergy is **weak**!
In vitro gastroduodenal digestion methods that use **physiological conditions** may reveal more information about protein presentation to the gastrointestinal epithelium in a physiologically relevant context.

Measurement of protein digestibility **should not be regarded as a stand-alone endpoint** for the safety assessment of novel proteins (Ladics, 2019).


PERSPECTIVE article

Front. Bioeng. Biotechnol., 17 September 2021
Sec. Biosafety and Biosecurity
Volume 9 - 2021 | https://doi.org/10.3389/fbioe.2021.747490

frontiers

Erroneous Belief that Digestive Stability Predicts Allergenicity May Lead to Greater Risk for Novel Food Proteins

Rod A. Herman[1]* Jason M. Roper[2]


ELSEVIER

Food and Chemical Toxicology
Volume 107, Part A, September 2017, Pages 88-98


Peanut digestome: Identification of digestion resistant IgE binding peptides

Luigia Di Stasio [a b], Gianluca Picariello [a], Mariantonietta Mongiello [a], Rita Nocerino [c], Roberto Berni Canani [c], Simona Bavaro [d], Linda Monaci [d], Pasquale Ferranti [b], Gianfranco Mamone [a]

Risk assessment tools for allergenicity prediction: *in vitro* tools IgE binding

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IgE binding assays, such as radio or enzyme allergosorbent assays (RAST or EAST), enzyme-linked immunosorbent assay (ELISA) or electrophoresis combined to immunoblotting with sIgE sera, are considered **adequate**.

To fulfil regulatory requirements, sera should be collected from very well-characterised allergic individuals with a **convincing clinical history** of allergy against a specific food and a cause-and-effect relationship between the consumption of the food, and the elicitation of allergic symptoms should be established by a **DBPCFC**.
Sera from individuals with allergies to non-phylogenetically related organisms (**negative controls**) should be used to exclude non-specific IgE binding.

The collection of significant volumes of serum in allergic patients, notwithstanding ethical considerations, constitutes a major bottleneck, particularly for rare allergens. From a future perspective, these practical and methodological obstacles could be overcome by using human-derived monoclonal IgE antibodies. Ideally, the building up of **a bank of monoclonal sIgE,** which could be used to detect allergenic proteins, is possible.

Risk assessment tools for allergenicity prediction: *in vitro* tools
Basophil activation test (BAT)

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The simultaneous use of a better test for functional IgE binding is advisable. Activation of **basophils** can be detected through upregulation of selected surface proteins measured by flow cytometry.

BAT was consistently proven to be **highly specific and highly sensitive**, particularly in food allergies. Thus, its use can dispense patients from a risky and stressful exposure to allergens during oral food challenges. Indeed, BAT can correctly predict the clinical outcome following exposure of allergic patients to specific allergens (elicitation).

Allergy EUROPEAN JOURNAL OF ALLERGY AND CLINICAL IMMUNOLOGY

REVIEW ARTICLE | Open Access

Basophil activation test: Mechanisms and considerations for use in clinical trials and clinical practice

Alexandra F. Santos, Oral Alpan, Hans-Jürgen Hoffmann

First published: 21 January 2021 | https://doi.org/10.1111/all.14747 | Citations: 75

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In vivo models to understand cellular and molecular mechanisms of sensitisation

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To date, the immune responses in rodents are **not predictive** for allergenicity, adjuvanticity or for the ranking of the strength of allergenic responses against proteins (Ladics et al., 2010).

Using *in vivo* models for GMOs and also for novel food allergenicity risk assessment is difficult due to many challenges. To date, the usefulness of *in vivo* models for predictive allergenicity risk assessment is uncertain because of the current lack of validated, predictive models for allergenicity in humans.

In vivo models could potentially improve risk assessment and facilitate the introduction of innovative/novel protein sources with a low risk of allergic sensitisation. However, it is currently **impossible** to use them in the allergenicity risk assessment because there are **no standardized predictive models**. Additionally, it would be ideal to avoid animals for the allergenicity risk assessment.

Agenda

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- Novel food allergy
- Approaches to allergenicity risk assessment: the ImpARAS COST action
- EFSA Scientific Opinion on allergenicity and protein safety assessment of food and feeds derived from biotechnology
- Insects as novel food allergens

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Insects as novel food allergens

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LIBERTÀ

NOTIZIE ▾ | LUOGHI ▾ | SERVIZI AI LETTORI ▾ | EVENTI ▾

Mangia un pezzo di focaccia e sta male. Primo piacentino allergico a farine di insetti

06 Agosto 2023

È allergico ai crostacei, mangia un pezzo di focaccia e subito sta male. Nell'impasto c'era la farina di grilli. È il primo caso di allergia alle farine di insetti registrato

Yellow mealworm

Tenebrio molitor

House cricket

Acheta domesticus

Migratory locust

Locusta migratoria

Lesser mealworm

Alphitobius diaperinus

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SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 5 October 2015

PUBLISHED: 8 October 2015

doi:10.2903/j.efsa.2015.4257

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Risk profile related to production and consumption of insects as food and feed

EFSA Scientific Committee

*The risk of allergies to insects in the case of insects as a source of food or feed proteins is **plausible**, and may be based on the existence of **common allergens** (pan-allergens) of arthropods such as arachnids, crustaceans (lobster, shrimp, crab), myriapods and insects. Similarly, allergens of molluscs and helminths are often very similar to those of insects and may lead to cross-allergies. The more or less close **phylogenetic relationships** between the different classes of arthropods may explain **sequence homologies** and similarities in structure constituting B cell epitopes in common allergens (pan-allergen), responsible for possible **cross allergy** between edible insects and other **arthropods**, **mites** (arachnids), **crustaceans** and non-edible insects (**cockroaches**). Insect consumption by individuals allergic to e.g. dust mites or shrimp could therefore well trigger allergic reactions associated with this **cross-reactivity**.*

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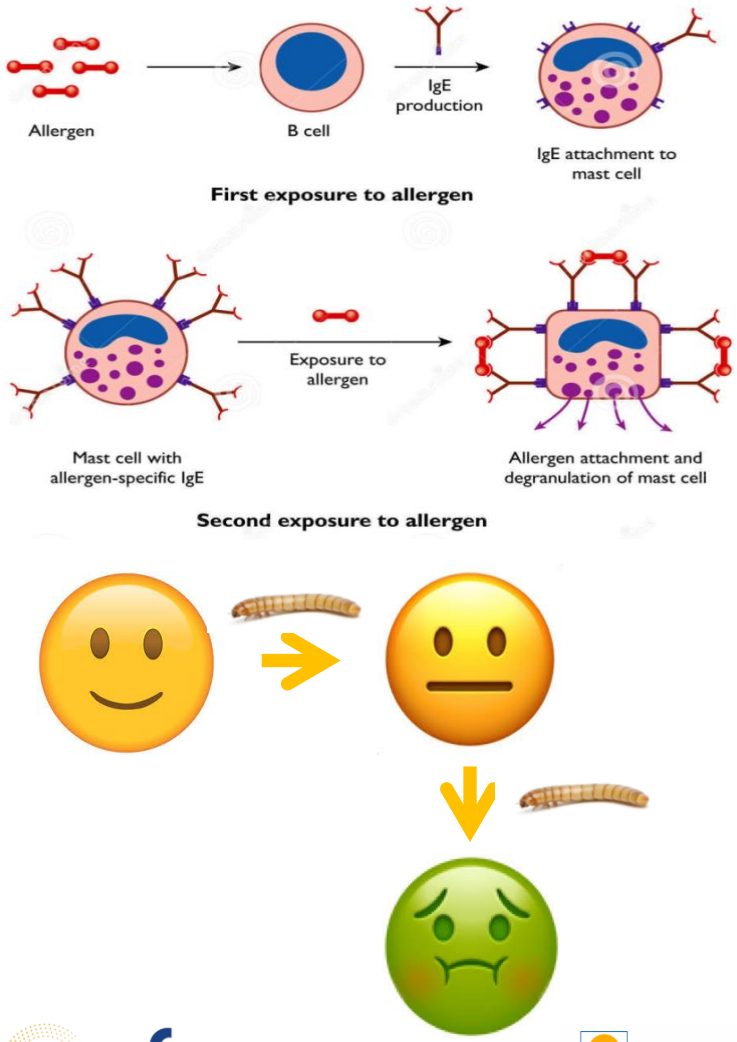
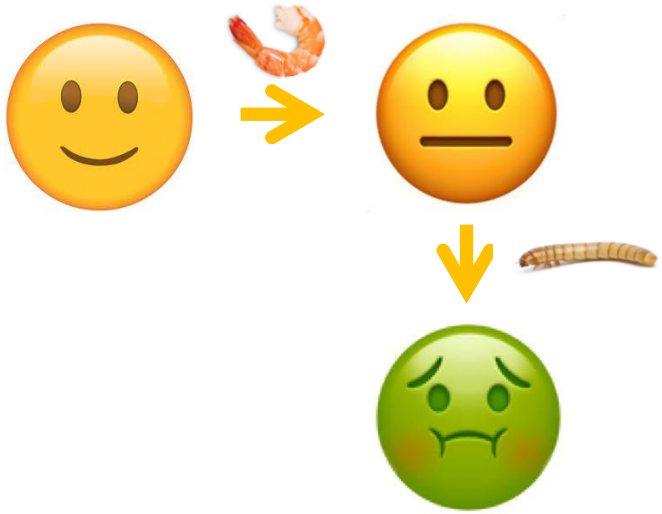
Primary sensitization *vs* cross-reactivity





?

Insect primary sensitization

Four Dutch mealworms farmers were sensitized to **mealworm**, confirmed by skin prick test (SPT), immunoblot and basophil activation test (BAT). Only one patient had an allergy to **house dust mites** (HDM). They underwent a double blind placebo controlled food challenge (DBPCFC) with **mealworm snacks and shrimps**. 2/4 subjects (50%) reported a history of food allergic symptoms to mealworm, which was confirmed in the DBPCFC, starting at a dose of 0.1 g of mealworm. **None of the subjects reacted to shrimp**. Mealworm exposure is a **risk** for developing food allergy to mealworm (*Broekman et al., J. Allergy Clin. Immunol. 2017, S0091–6749, 30340–30348*).

Exposure to larvae of *Tenebrio molitor* can lead to sensitization and subsequent development of allergic symptoms after ingestion of mealworms

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 24 November 2020

doi: 10.2903/j.efsa.2021.6343

Safety of dried yellow mealworm (*Tenebrio molitor* larva) as a

SCIENT

ADOPTED: 7

doi: 10.2903

Safet crick

SCIENT

ADOPTED: 2

doi: 10.2903

***domesticus*) powder as a novel food pursuant to Regulation (EU) 2015/2283**

SCIENTIFIC OPINION

EFSA Journal

ADOPTED: 25 May 2021

doi: 10.2903/j.efsa.2021.6667

Safety of frozen and dried formulations from migratory

protein, fat and fibre (chitin). The Panel notes that the levels of contaminants in the NF depend on the occurrence levels of these substances in the insect feed. The Panel notes that there are no safety concerns regarding the stability of the NF if the NF complies with the proposed specification limits during its entire shelf life. The NF has a high protein content, although the true protein levels in the NF are overestimated when using the nitrogen-to-protein conversion factor of 6.25, due to the presence of non-protein nitrogen from chitin. The applicant proposed to use the NF as whole, dried insect in the form of snacks, and as a food ingredient in a number of food products. The target population proposed by the applicant is the general population. The Panel notes that considering the composition of the NF and the proposed conditions of use, the consumption of the NF is not nutritionally disadvantageous. The submitted toxicity studies from the literature did not raise safety concerns. The Panel considers that the consumption of the NF may induce primary sensitisation and allergic reactions to yellow mealworm proteins and may cause allergic reactions in subjects with allergy to crustaceans and dust mites. Additionally, allergens from the feed may end up in the NF. The Panel concludes that the NF is safe under the proposed uses and use levels.

mealworm (*Alphitobius diaperinus* larva) as a Novel food pursuant to Regulation (EU) 2015/2283

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Innovative food products

COMMISSION IMPLEMENTING REGULATION (EU) 2023/58

of 5 January 2023

authorising the placing on the market of the frozen, paste, dried and powder forms of *Alphitobius diaperinus* larvae (lesser mealworm) as a novel food and amending Implementing Regulation (EU) 2017/2470

1. The frozen, paste, dried and powder
placed on the market within the Union.

The frozen, paste, dried and powder forms
set out in Implementing Regulation (EU) 20

2. The Annex to Implementing Regul
Regulation.

(1) in Table 1 (Authorised novel foods), the following entry is inserted:

Authorised novel food	Conditions under which the novel food may be used		Additional specific labelling requirements	Other requirements	Data protection
'**Frozen, paste, dried and powder forms of *Alphitobius diaperinus* larvae (lesser mealworm)**	Specified food category	Maximum levels (g/100g)	1. The designation of the novel food on the labelling of the foodstuffs containing it shall be "Frozen/paste *Alphitobius diaperinus* larvae (lesser mealworm)" or "Dried/powder *Alphitobius diaperinus* larvae (lesser mealworm)" depending on the form used. 2. The labelling of food supplements containing the novel food shall bear a statement that those food supplements should not be consumed by persons under 18 years of age. 3. The labelling of the foodstuffs containing frozen, paste, dried or powder forms of *Alphitobius diaperinus* larvae (lesser mealworm) shall bear a statement that this ingredient may cause allergic reactions to consumers with known allergies to crustaceans, and products thereof, and to dust mites. This statement shall appear in close proximity to the list of ingredients.		Authorised on 26.1.2023. This inclusion is based on proprietary scientific data protected in accordance with Article 26 of Regulation (EU) 2015/2283. Applicant: Ynsect NL B.V, Harderwijkerweg 141B, 3852 AB Ermelo, the Netherlands. During the period of data protection, the novel food is authorised for placing on the market within the Union only by Ynsect NL B.V., unless a subsequent applicant obtains authorisation for that novel food without reference to the proprietary scientific data protected in accordance with Article 26 of Regulation (EU) 2015/2283, or with the agreement of Ynsect NL B.V. End date of the data protection: 26.1.2028.'
	Cereal bars	25 (Dried form) 25 (Powder form)			
	Bread and rolls	20 (Powder form)			
	Processed and breakfast cereals	10 (Dried form) 10 (Powder form)			
	Porridge	15 (Powder form)			
	Pre-mixes (dry) for baked products	10 (Powder form)			
	Dried pasta-based products	10 (Powder form)			
	Stuffed pasta-based products	28 (Frozen or paste form) 10 (Powder form)			
	Whey powder	35 (Powder form)			
	Soups	15 (Powder form)			
	Cereal-, pasta-based dishes	5 (Powder form)			
	Pizza-based dishes	5 (Dried form) 5 (Powder form)			
	Noodles	10 (Powder form)			
	Snacks other than chips	10 (Dried form) 10 (Powder form)			

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EU-FORA SERIES 5

EFSA Journal

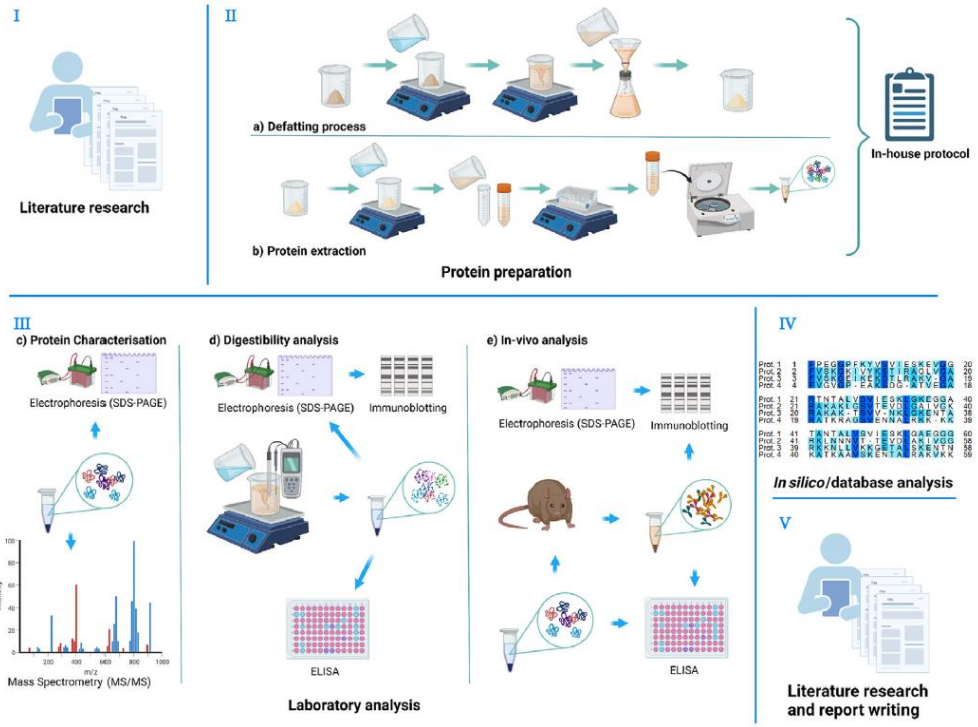
APPROVED: 31 August 2022

doi: 10.2903/j.efsa.2022.e200910

Novel foods: allergenicity assessment of insect proteins

Biase Liguori, Ana Isabel Sancho, Morten Poulsen and Katrine Lindholm Bøgh

National Food Institute, Technical University of Denmark, Lyngby, Denmark



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Allergenicity assessment of black soldier fly larvae as sustainable novel food

A.I. Sancho[1]; B. Liguori[1]; H. Bundgaard Larsen[1]; M. Lübeck[2]; K. Lindholm Bøgh[1]

[1]Research Group for Food Allergy, National Food Institute, Technical University of Denmark, Kgs. Lyngby, Denmark; [2]Department of Chemistry and Bioscience, Aalborg University, Aalborg, Denmark

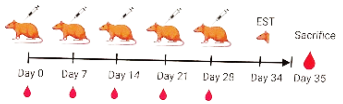
BACKGROUND

Insects represent a promising novel and sustainable source of dietary proteins. Before novel food proteins can be placed in the market, it is important to assess their allergenicity. The aim of this study was to evaluate the *de novo* sensitising capacity of black soldier fly larva (BSFL) (*Hermetia illucens*) proteins as well as their cross-reactivity to shrimp proteins in an animal model of food allergy.

METHODS

Rats (n=8/group) were immunised i.p 5 times with either PBS, as control, or four different doses of BSFL, peanut (control high allergenic), or spinach (control low allergenic) protein extracts **(Fig. 1)**. Specific IgG1 and IgE were analysed by ELISAs, and the clinical reactivity assessed by an ear swelling test (EST). The BSFL protein profile and immunoreactivity were determined by SDS-PAGE and immunoblotting, respectively. Cross-reactivity between BSFL and shrimp proteins was evaluated by ELISA and immunoblotting. Further, BSFL protein *in vitro* digestibility studies were performed.

Figure 1. Animal experimental design. Groups of Brown Norway rats (n=8) were i.p immunised 5 times with either PBS or 12.5 µg, 50 µg, 125 µg or 500 µg of either BSFL, peanut as high-allergenic control or spinach as low-allergenic control at Day 0, 7, 14, 21 and 28. At Day 34 an ear swelling test was performed and at Day 35 rats were sacrificed. Figure created with BioRender.com



RESULTS

Immunogenicity and sensitising capacity:

BSFL proteins showed immunogenicity as well as sensitising capacity **(Fig. 2)**. BSFL proteins induced statistically significant lower levels of specific IgG1 and IgE compared to peanut, and statistically significant higher IgG1 levels compared to spinach **(Fig. 3A, B)**. BSFL induced IgE levels comparable to that of spinach **(Fig. 3B)**. The ear swelling test results seemed to indicate the development of functional IgE of clinical relevance **(Fig. 3C)**.

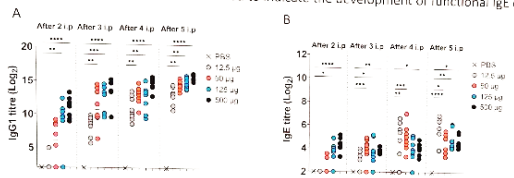


Figure 2. Specific IgG1 (A) and IgE (B) raised in groups of rats i.p immunised 5 times with either PBS or four different doses of BSFL extract. Each symbol represents a rat and horizontal lines indicate median. Kruskal-Wallis test was performed. Statistically significant differences are shown as: *p<0.05, **p<0.01, ***p<0.002, ****p<0.0001.

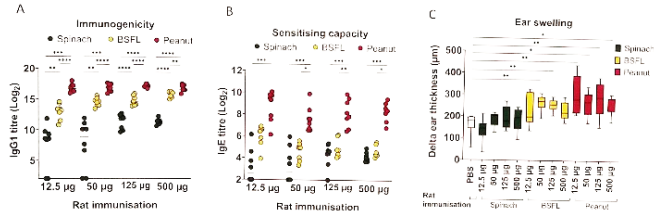


Figure 3. Comparison of the immunogenicity and sensitising capacity of BSFL, peanut and spinach extracts. Rats were i.p immunised 5 times with four different doses of BSFL, peanut or spinach extracts and sera specific IgG1 (A) and IgE (B) levels were determined by ELISA. An ear swelling test (C) was performed. Each symbol represents a rat and horizontal lines indicate median. Kruskal-Wallis test was performed. Statistically significant differences are shown as: *p<0.05, **p<0.01, ***p<0.001, ****p<0.0001.

Cross-reactivity and impact of *in vitro* gastroduodenal digestion:

Shrimp-specific IgG1 and IgE reactivity against BSFL protein was ~10-fold and ~4-fold lower than the IgG1 and IgE reactivity against shrimp proteins **(Fig. 4A, B, C)**. The IgG1 binding capacity of BSFL proteins seemed reduced upon *in vitro* gastroduodenal digestion as determined by ELISA **(Fig. 5A)** and immunoblotting **(Fig. 5B)**.

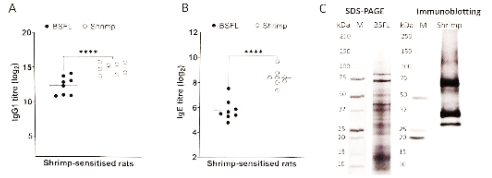


Figure 4. Cross-reactivity between BSFL and shrimp protein extracts. Cross-reactivity by means of IgG1 (A) and IgE (B) ELISAs with sera raised against shrimp and tested against BSFL. BSFL protein profile and IgG1 reactivity of a pool of sera from shrimp-sensitised animals towards BSFL by SDS-PAGE and immunoblotting (C). M: Molecular weight marker. Each symbol represents a rat and horizontal lines indicate median. T-test analysis was performed. Statistically significant differences are shown as: ****p<0.0001.

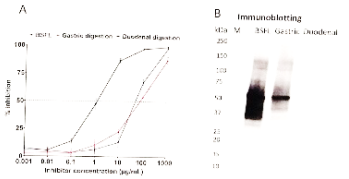


Figure 5. Impact of *in vitro* gastrointestinal digestion. IgG1 inhibitory ELISA (A) with sera from BSFL immunised rats. Inhibition with either intact protein, gastric or duodenal digests. Immunoblotting (B) with sera from BSFL immunised rats for detection of proteins in either intact, gastric or duodenal digests.

CONCLUSIONS

This study suggests that BSFL proteins have an inherently low level of allergenicity compared to that of peanut proteins, and that ingestion of BSFL may pose a low risk of inducing allergic reactions in shrimp allergic individuals.

The authors wish to thank Alan R. Mackie and Neil M. Rigby (University of Leeds, Leeds, United Kingdom) for providing the peanut extract.

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How to diagnose a food allergy?

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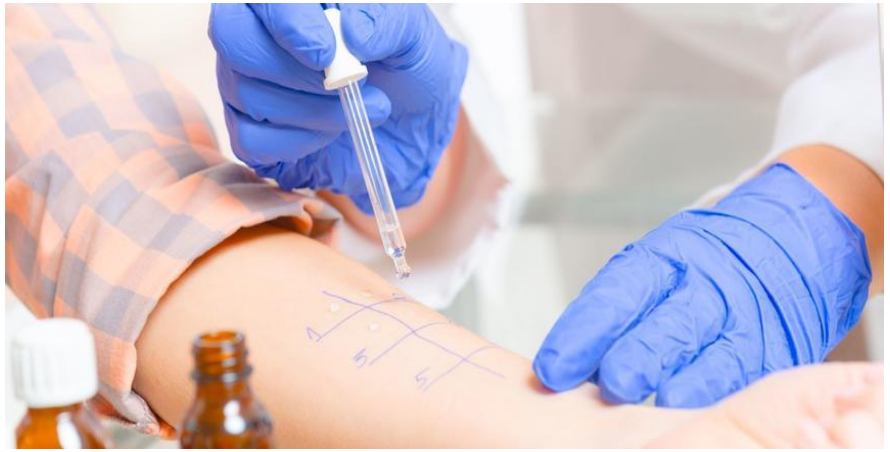
IgEs in the blood are not fully predictive of clinical symptoms, just of sensitization



In vivo Skin Prick Test (SPT) is considered a reliable screening method to diagnose IgE-mediated allergic disease in patients with rhinoconjunctivitis, asthma, urticaria, anapylaxis, atopic eczema and suspected food and drug allergy *(Heinzerling et al., Clin Transl Allergy 2013; 3: 3)*

Oral food challenge is the only reliable tool to diagnose a food allergy. In Double Blind Placebo Controlled Food Challenges (DBPCFC) a selected group of clinically characterized allergic individuals is challenged with **defined increasing doses** of the allergenic substance disperse in a food and with placebo controls (same food without the allergenic substance).

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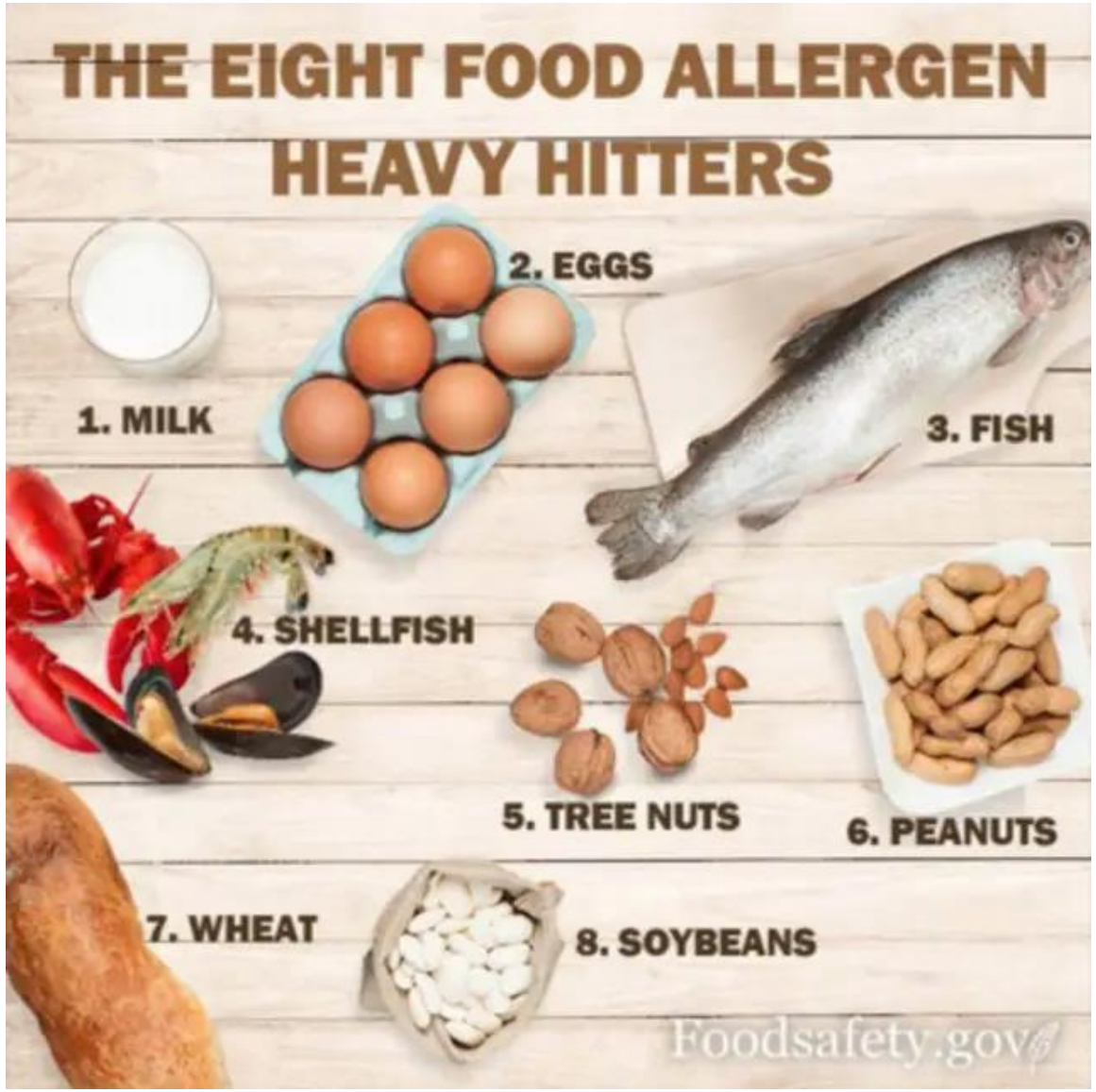
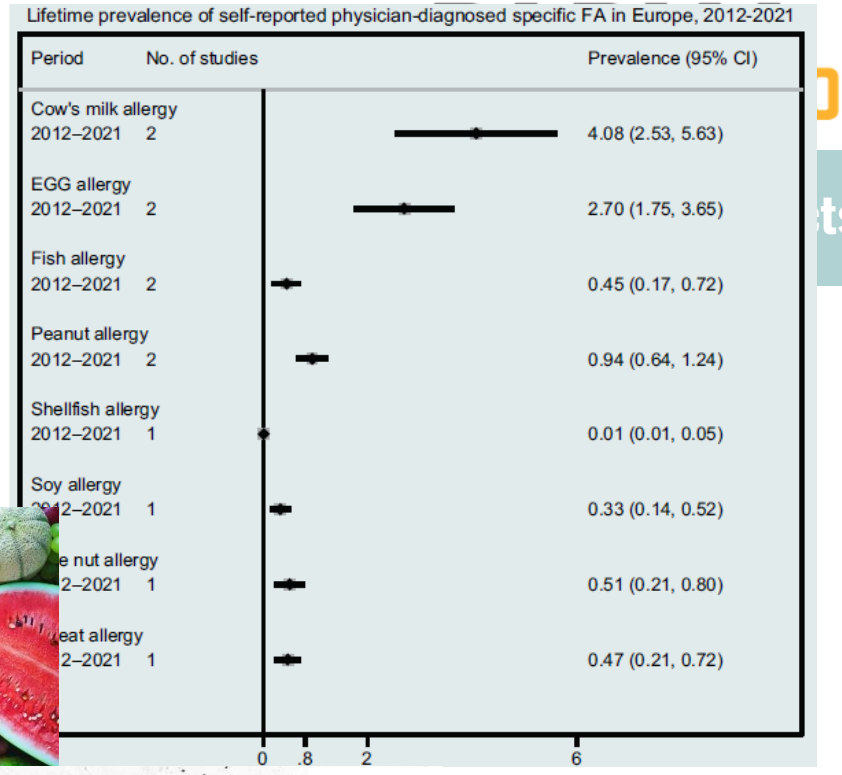


Pooled estimates for self-reported physician-diagnosed food allergy to the eight common foods in Europe for lifetime prevalence between 2012 and 2021 *(Spolidoro et al., Allergy, 2023)*.



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Determinants of food protein allergenicity

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Environmental factors, like routes of exposure, timing of exposure, microbial exposure, oral and gut microbiota composition in case of oral exposure, epithelial barrier integrity and/or non-allergenic components of the food matrix such as immune-modulating components (adjuvants) of allergenic sources may facilitate T helper 2 (Th2) immune responses.

Possible links between the **proteins' biological function**/activity and their allergenicity are emerging (Ozias-Akins & Breiteneder, 2019; Foo and Mueller, 2021).

Other routes of exposure besides the oral one may also be relevant for sensitisation (Wavrin et al. 2015; du Toit et al., 2016; van Bilsen et al., 2017).

Heat treatments induce chemical/physical modifications, which may affect the stability of enzymatic digestion and, consequently, the allergenicity of food proteins to a varying extent, depending on the time and temperature (Di Stasio et al., 2020).

In vitro tools to understand cellular and molecular mechanisms of sensitisation

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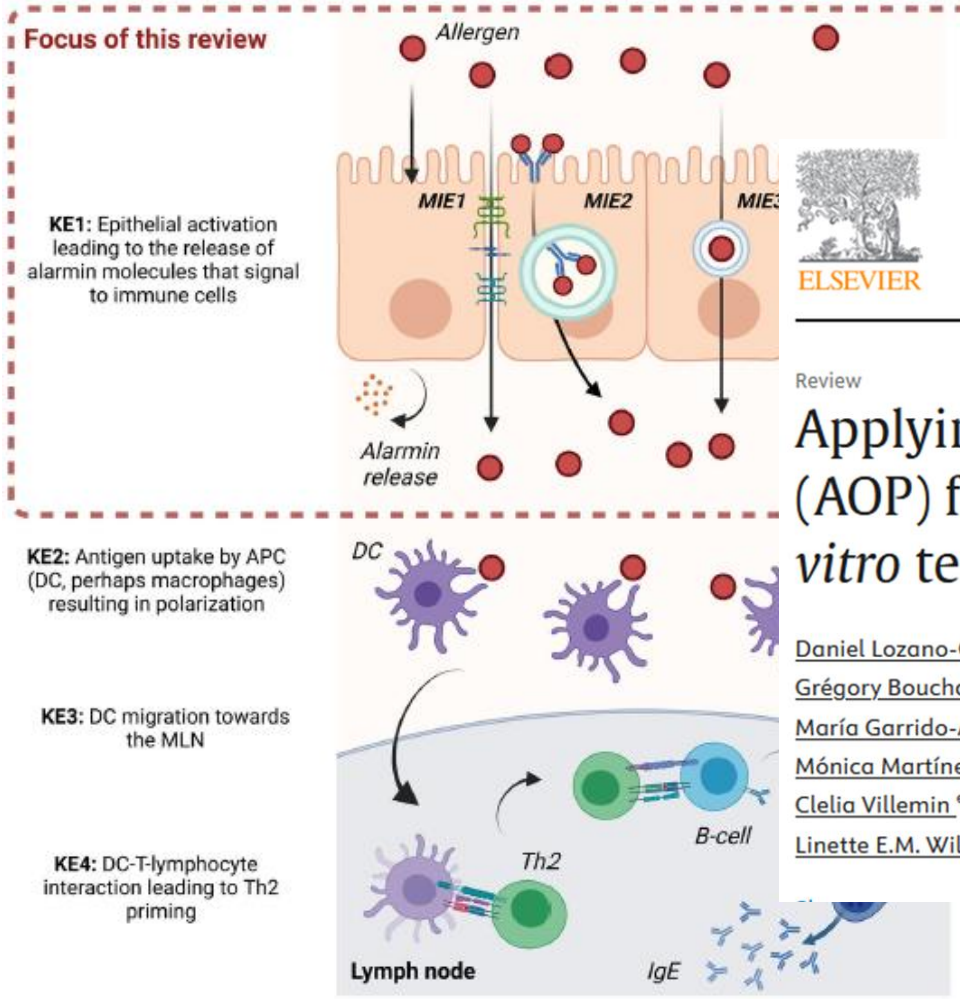

ELSEVIER

Trends in Food Science & Technology

Volume 85, March 2019, Pages 307-319

Review

Applying the adverse outcome pathway (AOP) for food sensitization to support *in vitro* testing strategies

Daniel Lozano-Ojalvo [a], Sara Benedé [b], Celia M. Antunes [c], Simona L. Bavaro [d], Grégory Bouchaud [e], Ana Costa [c], Sandra Denery-Papini [e], Araceli Díaz-Perales [f], María Garrido-Arandia [f], Marija Gavrovic-Jankulovic [g], Simone Hayen [h], Mónica Martínez-Blanco [i], Elena Molina [i], Linda Monaci [d], Raymond H.H. Pieters [j], Clelia Villemin [e], Harry J. Wichers [k], Barbara Wróblewska [l], Linette E.M. Willemsen [m], Erwin L. Roggen [n] ...Jolanda H.M. van Bilsen [o]

Dijk et al., Compr. Rev. Food Sci. Food Saf. 2023

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Acceptable levels and threshold values of food allergens

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Thresholds are a characteristic of the hazard that allergenic foods present to the food-allergic population. Their establishment is essential to the evidence-based application of risk management and mitigation strategies, such as Precautionary Allergen Labelling (PAL) (*FAO and WHO, Codex Alimentarius Commission, 2021. Summary report of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens. Part 2: Review and establish threshold levels in foods of the priority allergens. FAO, Rome*).

The FAO/WHO Expert Committee on risk assessment of food allergens has agreed that, for a series of priority allergenic food sources, the objective of minimising 'to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response' could be met by defining reference doses (RfDs) based on dose distribution modelling of minimum eliciting doses (MEDs) and supported by data on the severity of symptoms. The Committee agreed the safety objective could be met for RfD's corresponding to eliciting doses predicted to result in objective reactions in no more than 5% (ED05) of the allergic population.

A taxonomic view

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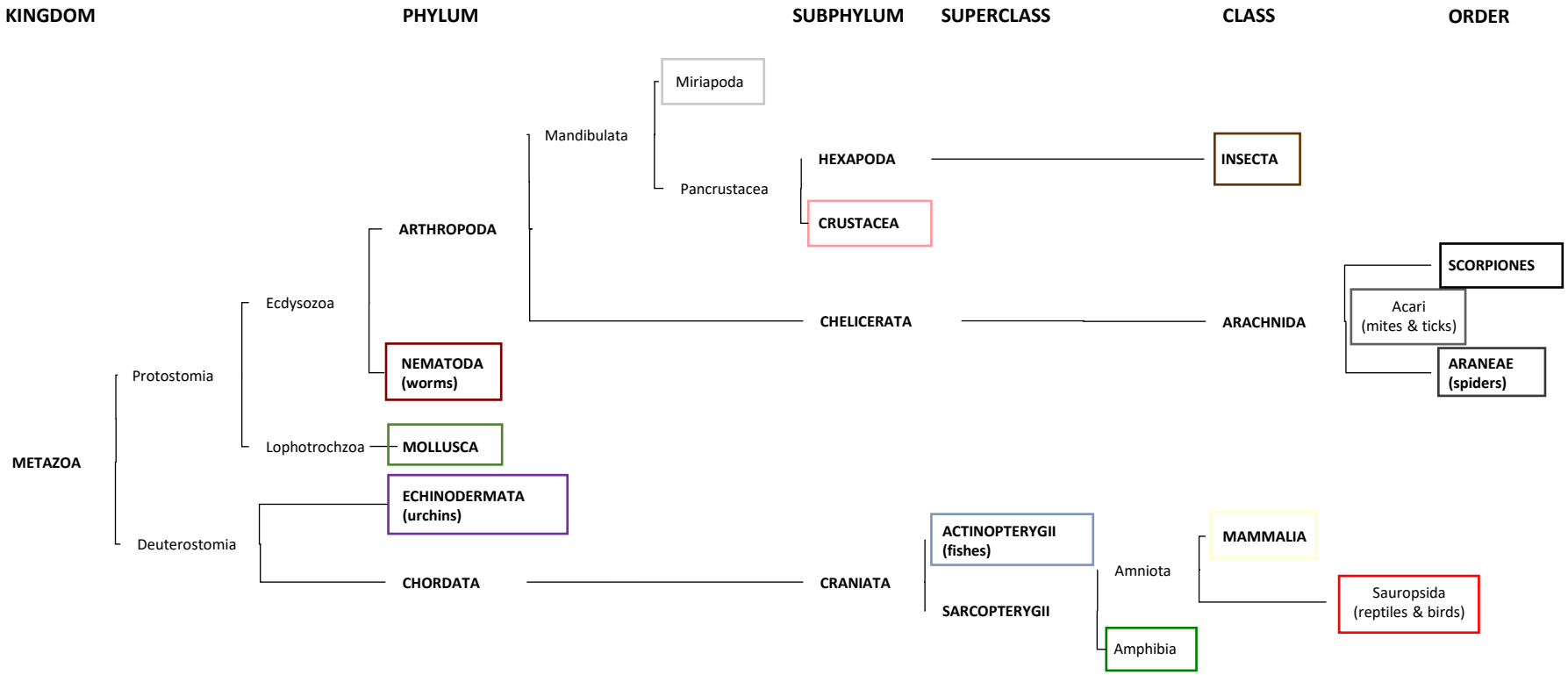

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WG3: *In vivo* methods to predict sensitisation

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Bøgh *et al. Clin Transl Allergy* (2016) 6:21
DOI 10.1186/s13601-016-0110-2

Clinical and Translational Allergy

REVIEW Open Access

Current challenges facing the assessment of the allergenic capacity of food allergens in animal models

Katrine Lindholm Bøgh[1], Jolanda van Bilsen[2], Robert Głogowski[3], Iván López-Expósito[4], Grégory Bouchaud[5], Carine Blanchard[6], Marie Bodinier[5], Joost Smit[7], Raymond Pieters[7], Shanna Bastiaan-Net[8], Nicole de Wit[8], Eva Untersmayr[9], Karine Adel-Patient[10], Leon Knippels[11,12], Michelle M. Epstein[13], Mario Noti[14], Unni Cecilie Nygaard[15], Ian Kimber[16], Kitty Verhoeckx[2] and Liam O'Mahony[17*]

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Conclusions and Recommendations

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It is **unrealistic** that a **single test** will, in short/medium term, be predictive of allergenicity. Therefore, the 'weight-of-evidence' approach for allergenicity assessment is still valid, although the evidence needed might differ depending on whether a conventional GMO or another type of new biotech food is being assessed.

Current guidelines in the Codex Alimentarius, initially published in 2003, focused on food derived from existing 'modern' biotechnology available at the time and **requires updating**.

The draft of a roadmap to (re)define the allergenicity safety objectives and risk assessment will be needed to address the key questions for risk assessors and risk managers:
(1) what is the purpose of the allergenicity risk assessment?
(2) what is to be assessed in the allergenicity assessment?
(3) what level of confidence do we need for the predictions?
(4) what is considered an unacceptable/acceptable risk in the allergenicity risk assessment?

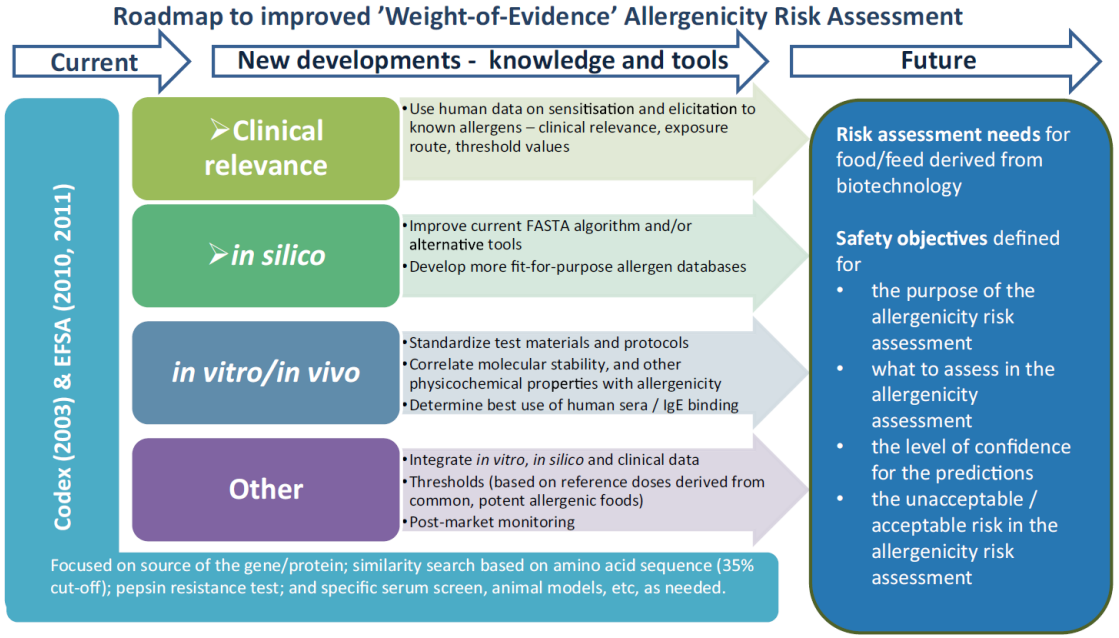

Figure 1: Roadmap to improved 'Weight-of-Evidence' Allergenicity Risk Assessment

EUROPEAN FOOD SAFETY AUTHORITY

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