Food Innovation and Advances

REVIEW

Open Access

https://doi.org/10.48130/FIA-2023-0015

Food Innovation and Advances **2023**, 2(2):115–123

Overview of allergenic risk of novel foods

Zhuo Chen[1,2,3,4,5], Wenfeng Liu[1,2,3,4], Jian Wang[1,2,3,4], Dongxia Yan[1,2,3,4], Hua Feng[1,2], Yong Wu[1,3,4], Yongning Wu[6] and Hongbing Chen[1,3,4*]

[1] *State Key Laboratory of Food Science and Resources, Nanchang University, Nanchang, 330047, Jiangxi, China*
[2] *School of Food Science and Technology, Nanchang University, Nanchang 330031, Jiangxi, China*
[3] *Sino-German Joint Research Institute, Nanchang University, Nanchang 330047, Jiangxi, China*
[4] *Jiangxi Province Key Laboratory of Food Allergy, Nanchang University, Nanchang 330047, Jiangxi, China*
[5] *College of Pharmacy, Gannan Medical University, Ganzhou 341000, Jiangxi, China*
[6] *NHC Key Lab of Food Safety Risk Assessment, China National Center for Food Safety Risk Assessment (CFSA), Beijing 100022, Beijing, China*
* Corresponding author, E-mail: chenhongbing@ncu.edu.cn

Abstract

The reported cases of food allergies are steadily increasing. With the invention of more novel foods, new and unfamiliar allergens are being introduced into our diets, which raises concerns about the potential risk of novel food allergies. The purpose of this review is to assess the allergenic risks associated with novel food components, strategies for assessing risk in relation to novel food allergens, and current regulations for managing food allergens in novel food products.

Citation: Chen Z, Liu W, Wang J, Yan D, Feng H, et al. 2023. Overview of allergenic risk of novel foods. *Food Innovation and Advances* 2(2):115–123 https://doi.org/10.48130/FIA-2023-0015

Introduction

With the advance of innovation and globalization, people have access to a diverse range of food sources and have increasingly complex nutritional requirements, emphasizing the urgent need to establish sustainable and healthy food systems[1,2]. Novel food is a highly nutritious, sustainable alternative to conventional foods. According to the Food and Agriculture Organization and World Health Organization (FAO/WHO), new foods are those that have not been widely consumed and can be novel through recent technological innovations or due to historical restrictions in certain regions and populations[3].

Diversifying protein sources by substituting is one approach that can have both nutritional and environmental benefits[2,3]. Advances in food technology have made it possible to expand the sources, types, and ranges of food raw materials, resulting in a vast array of novel foods[4]. In scientific research, two interrelated trends that have received significant attention are meat alternatives and products for promoting health and wellness[5]. Novel foods encompass a variety of forms, including plant-based foods, insect-based foods, cultured meat, 3D printed foods, microbial fermentation-derived ingredients, algae, and nano foods, among others[4,6,7]. It is also worth noting that transgenic foods are sometimes considered a class of new foods[6].

Allergies are immune-mediated diseases caused by food allergens[8,9]. It can be classified into two types based on the immunological mechanism: IgE-mediated or non-IgE-mediated[7,8]. IgE-mediated food allergy occurs in two stages[10,11]: Sensitization and challenge. During sensitization, the allergen activates dendritic cells, which stimulate the differentiation of naïve $CD4^+$ T cells into Th2 cells. The Th2 cells then secrete cytokines, thereby causing B cells to produce specific IgE[10,11]. In response to allergen cross-linking, specific IgE binds to effector cells such as mast cells and eosinophils, which release inflammatory factors like histamine[10,11]. This leads to the appearance of food allergy symptoms[10,11]. In this stage, the allergen binds to specific IgE by epitope (known as antigenic determinant). Therefore, allergens containing similar antigenic determinants can induce food allergy by cross-reaction. The simple mechanism of IgE-mediated food allergy is shown in Fig. 1. Non-IgE- mediated food allergy occurs much later than the time of allergen uptake and often has delayed symptoms. Typical non-IgE-mediated food allergy conditions include enterocolitis syndrome, and eosinophilic esophagitis[12,13].

Food allergies have significant impacts on consumers' health and safety. Food allergies are characterized by urticaria, nausea, angioedema, oropharyngeal pruritus, as well as digestive and respiratory problems[8,9,14]. Symptoms of food allergies, such as IgE-mediated anaphylactic shock, can be life-threatening[8,9,14]. There are currently no drugs approved by regulatory bodies for food allergy treatment, except for Palforzia, a certain peanut allergen powder specific to peanut allergies[14,15]. Food allergies are managed with antihistamines and auto-injectors in the case of acute allergic reactions, and allergy patients should avoid the uptake of allergens[13,15]. Therefore, besides significantly impacting the quality of life of patients, food allergies also have a financial impact on society. Insufficient protein intake can cause nutritional deficiencies, posing a threat to food safety[16]. Children in developed countries are becoming increasingly allergic to more than one type of food, with up to 40% affected[8,13]. Babies with atopic dermatitis who drink regular milk containing allergens will pay thousands of dollars over 6 years in disease-related medical expenses[17].

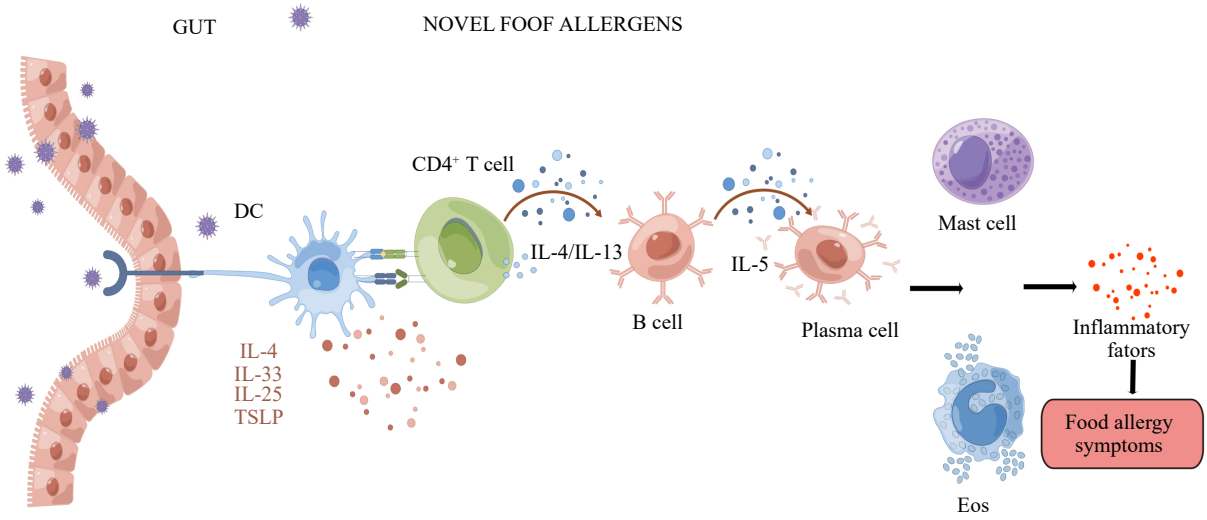

Fig. 1 The simple mechanism of IgE-mediated food allergy. (Drawn by Figdraw).

Across developed Western countries, food allergies have become more prevalent, while attention to novel foods has increased.[12,13,18,19]. It is crucial, however, to assess the potential allergy hazards of novel foods before introducing them to humans[20–23]. Food allergens accounted for the highest percentage among the top four hazards, namely biological contamination, physical contamination, chemical contamination, and undeclared food allergens. Between 2008 and 2018, undeclared food allergens accounted for 46.5% of all food safety incidents and recalls worldwide[24]. Several countries have placed novel food safety management on their agendas, issuing relevant regulations, guidelines, or legal frameworks[25–27]. However, predicting the potential allergenicity of novel food remains challenging[23].

Allergenic risk of components in novel foods

Protein

Novel foods are rich in proteins as an innovative and sustainable human and animal nutrition source. Technology like bioflocculation and protein concentrate can increase the unit weight of the product in protein content[28–30]. The most common allergens in food allergies are proteins, and many researchers believe food allergy is an immune-mediated reaction caused by harmless dietary proteins[21,30,31].

The alternative protein industry has made rapid progress in recent years. Some companies call alternative proteins new food[32]. Plant leaves, microalgae, and edible insects all provide a large number of novel proteins[33,34]. Edible insects are good alternative proteins, but they are also as new allergen source[32]. Novel food proteins that conform to the physical and chemical properties of 10-70 kDa size, heat resistance, digestion resistance, and high water-solubility are often regarded as potentially allergenic food proteins[22]. However, the immune system recognizes protein antigens and the activation of effector cells is achieved not through the whole protein but through the epitopes contained in the protein. A protein can have multiple epitopes, and common food allergen proteins can have up to over a hundred. According to the Epitope Information Resource Library (IEDB, www.iedb.org), Th2 cell epitopes are usually linear peptides composed of 8-26 amino acids, and B cell linear epitopes are generally 8-15 amino acids long. Moreover, conformational epitopes are only small parts of the three-dimensional structure of proteins, and common food allergens in the epitopes can have hundreds[10]. Protein has quaternary structure, at the same time that the structure of all levels is folded, and some epitopes that can be identified are not necessarily exposed to the surface of the protein structure. After the thermal processing or non-thermal processing common to novel food preparation, even if the novel food protein is not heat-tolerant and not resistant to enzymatic hydrolysis, it may be exposed to the allergen epitopes inside the protein, causing allergy. For example, C18 unsaturated fatty acids（UFAs) can effectively promote the gradual development of alpha-Lactalbumin (BLA) and beta-lactoglobulin (BLG) structures, improve their hydrophobicity, and then increase allergenicity[35]. There is also a case where food allergens are not heat tolerant, but their epitopes are heat-resistant, so food after processing still could cause allergy. Studies have confirmed that the potential marker of almonds allergen Pru du 6 is an epitope conformation epitope that is resistant to heat and *in vitro* digestion in the presence of a food matrix[36]. People normally tolerant to unmodified wheat products may be allergic to newly introduced epitopes after the deamidation of gluten[32]. It has been shown through double-blind placebo-controlled food challenges (DBPCFCs) that exposure to mealworms may induce *de novo* sensitization to larval cuticle proteins[32]. As a result, not all allergen proteins could be positively identified as allergenic with homology testing.

Carbohydrate

Carbohydrates are an important nutrient found in novel foods. According to the list of novel foods approved by the European Union, it is easy to find that the EU has approved multiple single-ingredient carbohydrates as novel foods[37–41]. Protein glycosylation and dietary fiber processing are two common novel food processing methods that can provide us with new carbohydrate foods[42–44]. Other natural novel resource foods can also provide carbohydrate nutrition, such as cranberry, and edible insect cricket powder[45,46]. However, carbohydrates considered safe and widely found in novel foods are

an allergenic risk due to cross-reactive carbohydrate determinants (CCD) binding to IgE and causing cross-reactivity[47].

Red meat allergic reactions are thought to be closely related to the specific IgE of disaccharide-galactose-α-1,3-galactose (α-gal)[48–50]. The Subcommittee on Allergen Nomenclature recently classified glycans as a potential allergic epitope on its website International Union of Immunological Societies (IUIS) ancillary section to describe classic CCDs as haptens.[47]. α-1,3-fucose, β-1,2-xylose, galactose-β-1,4-(galactose-β-1,4-galactose-β-1,6)-glucose are also typically B-Cell carbohydrate epitopes in foods[11]. However, glycans as allergens are controversial. Recently, a research result showed that the reactivity of N-glycan subsets carrying core α-1,3-fucose inversely correlates with asthma[51].

Lipids

The design of novel foods is based on nutritional value[43,52]. Lipids are another kind of essential nutrient[53,54]. Lipids are often used as essential components in creating novel foods, for example, glycolipids, phospholipids, short-chain fatty acids, unsaturated fatty acids, etc.[55] Food allergy can occur through several immunological pathways[56]. They are important ingredients of some nano liposome foods[56]. In the case of skin exposure to nanomaterials, immunomodulatory effects may induce allergic reactions[57,58]. Glycolipids have the potential allergenicity due to their carbohydrate epitopes[59]. On the other hand, lipids can interact with proteins. That changes the structural properties of protein allergens, which may expose linear epitopes inside proteins and affect protein immunogenicity[35,60].

The threshold distribution is related to the state of the body, lipids could change the human internal environment. Researchers have conducted threshold dose distribution studies on milk, eggs, sesame, walnuts, cashews, peanuts, and other foods, indicating that the intake of protein exceeding the threshold dose will cause the consequences of food allergy[61,62]. Lipids could affect the digestibility of allergens, alters intestinal absorption, and reduces the bioavailability of protein allergens, changing the threshold for allergic reactions[56]. Allergen proteins can be inserted into phosphatidylcholine (PC) dependent acidic pH conditions to form vesicles-like molten globules, which facilitates the expansion of allergen amino acid side chains and protects allergens from digestion by digestive juices, promoting allergic diseases[56,63]. Lipids promote allergic diseases by mediating cellular communication events[64]. Long-term medium-chain triglyceride (MCT) -based feeding in animals stimulates the epithelium to release Th2 biased cytokines, like IL-25, IL-33, and thymic stromal lymphopoietin(TSLP), which activate food allergy signaling pathways and cause spontaneous allergy[64,65]. The food allergy process could be influenced by lipids, for example, intervening in the composition of gut microorganisms or intestinal microbial metabolism, increasing the host's intestinal permeability and breaking tolerance status[56,66].

Allergenic risk assessment

Novel food allergenic risk assessments are imperative for preventing severe symptoms in allergic consumers. The probability and severity of harmful health effects caused by one or more hazards in food are referred to as food risk[67]. Additionally, a classic toxicology paradigm states that risk is a product of exposure and hazard. During the first decade of this century, knowledge of individual sensitivities to food allergy grew. Observing thresholds in clinical food challenges in the oral diet of food-allergic individuals has been a useful method to assess the risk of foods that cause sensitization[68–70]. Food allergies are relatively common in humans, and dietary proteins usually contribute to the development and initiation of allergic reactions. With the growing population, there is an increasing need for protein food, including new sources that are not yet available. A new or modified protein may also pose a risk of *de novo* sensitization, leading to novel food allergies. Hence, implementing a comprehensive and systematic testing and assessment strategy is crucial for identifying and characterizing potential allergenic risks[71].

Weight-of-evidence-based approach to allergenic risk

In evaluating the allergenic risk of novel foods, an exposure criterion is a concentration in foods, heat stability, and digestive stability, while a hazard criterion is a structural similarity to known allergens and the history of safe use. Current risk assessment strategies emphasize that there is no single method for predicting the allergenicity of novel foods. Therefore, the weight-of-evidence-based approach is the most commonly used allergenic assessment strategy[72]. The core of the weight-of-evidence-based approach used for potential allergenicity evaluation is to compare the sequence of a new protein with that of an allergenic protein that causes an allergic reaction using bioinformatics[23]. The latest analytical techniques allow for an increasingly better interpretation of the bioinformatics of proteins, and the primary, secondary, and tertiary structures of proteins can be evaluated at the amino-acid level. Additionally, there are a number of databases that are used for predicting food allergenicity and assessing risk, varying in entry criteria and allergen entries. New foods' potential allergenicity is ranked based on the clinical relevance and quality of the scientific evidence. Patient serum IgE antibodies or animal antibody sera can be used to analyze allergenic activity. Moreover, the use of cellular assays to determine the functional allergenicity of food proteins and digestion assays to determine protein stability have also been found to be helpful. The processing of food and the interaction of the food matrix with allergenic proteins are also thought to influence allergenicity. The compelling evidence for the allergenicity of novel foods lies in clinical data, such as skin prick tests or oral challenges.

Two types of novel foods at allergenic risk

Two different types of novel foods should be assessed for their allergenic risk[73]. The first type contains a known or homologous structure with known allergens in the novel food, which presents cross-reactivity. A comparative assessment can be undertaken for this case, and the extent of cross-reactivity can be explored. The second type of novel food is one in which an allergic reaction is observed for a previously unknown allergen structure, with no homology to a known allergen structure[23]. Ideally, this situation could use known allergenic and known non-allergenic reference proteins from non-homologous sources. However, additional cellular assays and animal models must be developed and validated. In summary, a comprehensive and systematic testing and assessment strategy is required to identify and characterize the risks associated with *de novo* allergenicity associated with specific proteins, including aspects of exposure, intrinsic protein properties, and matrix/processing effects.

Identification technologies for allergenic risks of novel foods

Allergen analysis

Comparing the information from the analysis with standard allergens to determine whether novel foods are allergenic. Analysis methods of allergens can be divided into non-immunological analysis and immunological analysis. Since novel foods are not necessarily single-component foods and have been processed, matrix/processing effects and epitope masking will affect the analysis. Nevertheless, the challenge remains in choosing the appropriate method to evaluate allergenicity.

Non-immunological analysis of food allergens

Non-immunological analytical techniques involve mass spectrometry (MS), circular dichroism (CD), fourier transforms infrared (FTIR), X-Ray, and nuclear magnetic resonance (NMR)[74]. Mass spectrometry is an excellent tool for analyzing allergen structures and is an important qualitative and quantitative tool in proteomics research[75]. By using fragmentation settings in the MS collision cell, quantitative triple quadrupoles and ion trap (IT) systems offer identification and quantification possibilities. According to the Tothrall-Project, the quantification of multiple food allergens in standardized incurred food matrices has also been developed using an MS-based prototype method[74,76].

There are two analysis strategies for mass spectrometry analysis[77]. Targeted analysis can be used to analyze potential allergens and conduct risk assessments for new foods containing known allergens. Non-targeted analysis can be used to evaluate new foods with unknown allergens. Based on known allergen information, it involves less evaluation of sensitization risk. The 'bottom-up' shotgun analysis strategy involves digesting novel food proteins and analyzing allergen-specific peptides. The 'top-down' analysis strategy involves isolating proteins in new foods and evaluating the potential allergenicity of the intact protein.

Immunological analysis of food allergens

Currently, immunoassays are the preferred method for detecting and identifying food allergens[78]. Specific serum screening-IgE binding assays, pepsin resistance and *in vitro* digestibility tests, and culture systems with cell lines or explants of mucosa grown in monolayers are commonly used routine immunoassays at this stage.

They can be used to analyze the allergenic potential of novel food allergens. With the development of science and technology, some biosensors are used as potential allergen analysis tools for 'gut-on-a-chip' devices. For example, a biosensor platform powered by nanovesicles derived from immune cells for detecting food allergens[79]. This method selectively binds to allergens by immobilizing allergen-specific antibodies (α-whey protein-specific antibodies) or allergen-specific antibodies to allergenic mediators (histamine-specific antibodies) on the electrode surface. The current and/or voltage changes while combined when through the local surface. Cell lines and organs containing antibodies are still important *in vitro*[78]. Regardless of the data collection method, the biological receptor that is widely used in food allergen analysis biosensors is the antibody.

Allergenicity assessment in an animal model

Many living beings may suffer from food allergies, for example, humans and rodents. Therefore, mouse models of food allergy are currently considered the best predictor of food allergenicity for assessing the potential allergenicity of novel food proteins[20]. In mouse models, pathophysiological conditions of food allergy, such as behavioral changes, body temperature, auricle swelling, cytokine response to allergens, and passive or active skin allergic reactions can be simulated. Other pathological conditions such as intestinal mucous membrane, skin, lungs, immunoglobulins in serum, and T-cell populations can also be used to characterize the allergenicity of novel foods. However, different immune statuses of the body can cause varying sizes of allergic reactions, and the current model-making method needs to be improved. Researchers are seeking the most appropriate route of exposure and protein form to simulate the closest pathological state to reality, but the results are still suboptimal. Because mouse pathophysiology differs from human pathophysiology, existing animal-based methods cannot accurately predict clinical outcomes of allergy to novel food proteins[80]. For example, IgG1 can cause allergic reactions in mice but not in humans. While pigs and rats were used to evaluate allergenicity, they are not the main animal models and require further evaluation/validation of endpoints[74,80].

Bioinformatic tools

As mentioned earlier, bioinformatics tools are key to evaluating the allergenic potential of novel foods[81–84]. These tools can identify known allergens from novel food allergens by comparing their structures with those of standard allergens. Initially, software such as Interact iVenn can be used to identify common proteins. Next, analytical information about the proteins in novel foods can be obtained, and their functions can be annotated. Finally, protein identity and similarity can be calculated using an allergen database. The major open specialized allergen databases for allergens are listed in Table 1.

Bioinformatic tools can also predict the potential allergenicity of novel proteins, identify potential epitopes that could cause an allergic reaction, and determine whether a protein exhibits cross-allergenicity with other known allergens and proteins of interest[84]. Different bioinformatic tools and tactics are available for implementing each of these functions *in-silico*. The probability of cross-reaction is greater when the protein sequence has a higher homology. The European Food Safety Authority (EFSA) Panel has defined the homology criteria with known allergens to be at least 35% on a sliding window of 80 amino acids[84]. Alternatively, one can search for the same epitope peptides in the structure of novel food proteins. Proteins larger than 6-mer and 8-mer allergenic epitopes can also be considered to have potential allergenicity[84]. Moringa oleifera leaves are novel food[84]. Using bioinformatics, Brusic & Petrovsky recently identified an allergen-encoding sequence in the ingredient extracted from Moringa oleifera leaves[84]. Figure 2 provides a sample flowchart illustrating how this process can be implemented.

Allergenic risk assessment

Regulation in the European Union

The European Union (EU) released Regulation 2015/2283 on novel foods in November, where the 'Novel foods can be newly

Table 1. Major open databases for allergen.

Database	URL location	Maintained by
WHO/IUIS Allergen Nomenclature	www.allergen.org	WHO/IUIS Allergen Nomenclature Sub-Committee
Structural Database of Allergenic Proteins (SDAP)	fermi.utmb.edu/SDAP	The University of Texas Medical Branch, USA
AllergenOnline (FARRP Allergen Database)	www.allergenonline.org	University of Nebraska-Lincoln, USA
Comprehensive Protein Allergen Resource (COMPARE)	comparedatabase.org	Toxins and Bioinformatics Committee, Health, and Environmental Sciences Institute
Allergome Database	www.allergome.org	Allergy Data Laboratories, Italy
Allermatch Database	www.allermatch.org	WFSR - Wageningen University and Research and Bioscience - Wageningen University and Research, The Kingdom of the Netherlands
Allergen Database for Food Safety (ADFS)	https://allergen.nihs.go.jp/ADFS/database	The Division of Biochemistry and Immunochemistry of the National Institute of Health Sciences, Japan
AllFam	www.meduniwien.ac.at/allfam/	The Department of Pathophysiology and Allergy Research of the Medical University of Vienna, Austria
AllerBase	bioinfo.unipune.ac.in/AllerBase/Home.html	Bioinformatics Centre, Savitribai Phule Pune University (SPPU), India

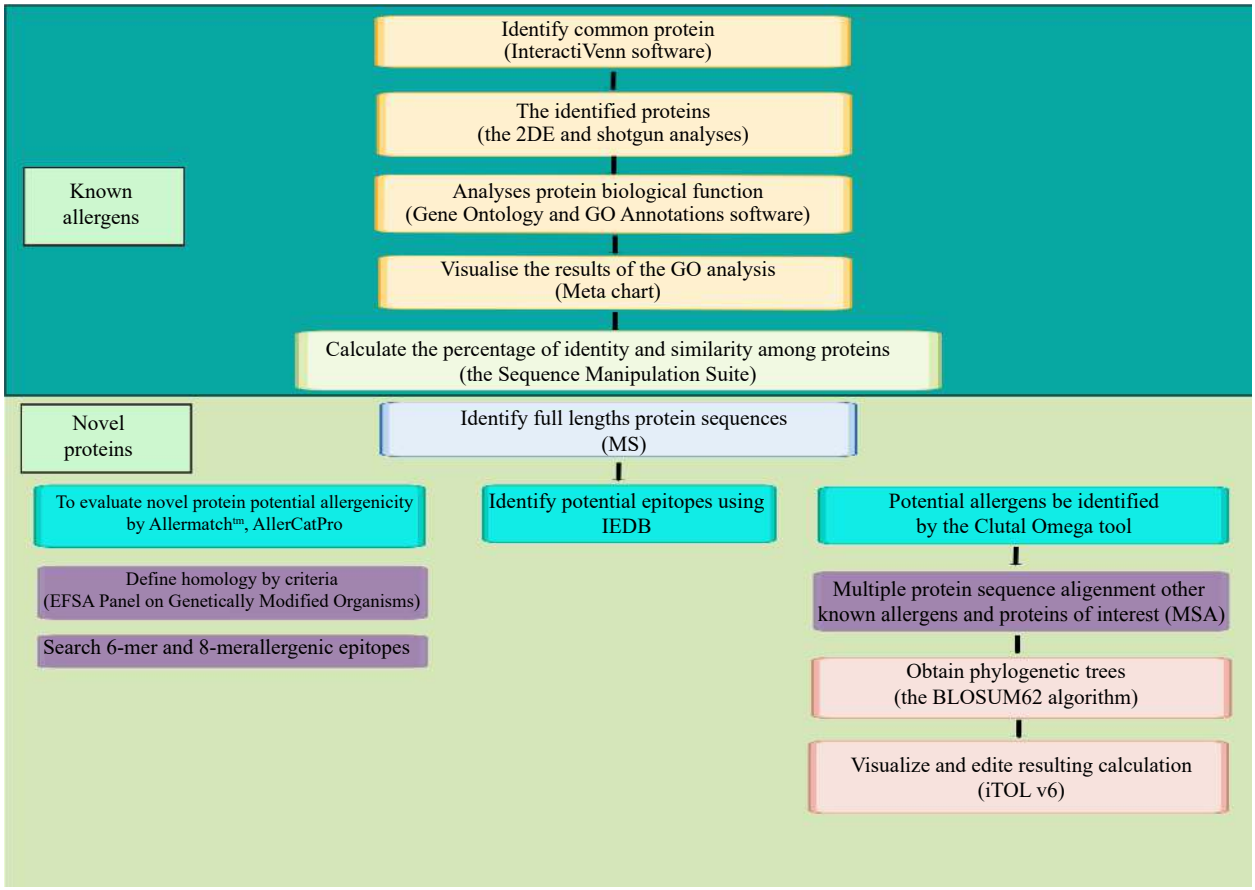

Fig. 2 Sample implementation flowchart: the allergen encoding sequences in a novel food ingredient from *Moringa oleifera* leaves were identified by bioinformatics tools[84]. (Drawn by Figdraw).

developed, innovative food, food produced using new technologies and production processes, as well as food which is or has been traditionally eaten outside of the EU'[85]. More specifically, there were ten categories considered novel foods produced from novel sources of ingredients and novel processing technologies. Moreover, novel food may also cover food consisting of certain micelles or liposomes and engineered nanomaterials.

EFSA Panel on Dietetic Products, Nutrition, and Allergies interpreted this regulation[71]. The panel experts indicated that the allergenicity assessment of novel foods should start with a qualitative or quantitative test to analyze whether the novel foods contain proteins. The potential allergenicity of proteins-free novel food is very low since most food allergens are proteins. When it comes to novel foods containing proteins, allergenicity is assumed by default[71]. Conducting literature reviews to gather information about allergenicity, allergic reactions, and/or allergenic studies (*in vitro*, *in vivo*) for assessing the potential allergenicity of new products and ingredients[71].

Regulation in the United States

There were no specific definitions and regulations for novel foods in the United States. Instead, novel foods are regulated as

ordinary foods[86]. The regulations are regardless of novel foods' technological, temporal, or geographical origin[86]. The FDA considers any novel food ingredient, either a food additive or Generally Recognized as Safe (GRAS), for specific uses. Nevertheless, the FDA still performed prophylactic research on the safety, regulation, and labeling of novel food to protect consumers and make regulatory recommendations and decisions.

Regulation in Canada

An overview of novel foods published by Health Canada defined it as products that are new or modified from existing foods, which may include substances not yet used as food, foods produced by novel processing techniques, and foods derived from genetically modified plants, animals, or microorganisms[25]. In July 2022, Health Canada updated the Guidelines for the Safety Assessment of Novel Foods[87], illustrating the allergenicity of novel foods of plant and microbial origin in terms of raw materials, novel processing technologies, and genetic modification[87]. For raw materials with no history of safe use, the preliminary strategy for assessing the allergenicity would be to investigate whether plants are relevant to allergic response[87]. Proteins from an allergenic source should not be added to foods where identity preservation is not guaranteed. Regarding the novel foods produced by novel processing technologies, the preliminary strategy would be to prevent accidental and unavoidable exposure of allergic individuals to food allergens[87], and the allergenicity should be re-evaluated when novel processing technologies were applied to foods containing allergenic proteins and resulted in changes in protein content. Moreover, the allergenic potential of the novel foods produced by genetically modified technology to cross-react with known food allergens or to cause hypersensitivity reactions needs to be assessed[87].

Regulation in Australia and New Zealand

Food Standard Australia and New Zealand (FSANZ) define novel foods as those that are not considered to be traditional and/or are produced using non-traditional processing techniques, and these foods designated as novel must undergo a public health and risk assessment before they can be approved for sale[88]. There is currently no specific guidance on the risk of allergenicity of novel foods in the relevant FSANZ documents, or the Australian New Zealand Food Standards Code[89].

Regulation in China

In 2013, China implemented the Measures for Examination of the Safety of New Food Ingredients, in which new food ingredients refer to relevant foods that are not traditionally consumed in China, including animal, plant, and microbial foods, ingredients isolated from animals, plants, and microorganisms, food ingredients whose original structure was changed, and other newly developed food ingredients[90]. In China, the use of new food ingredients requires the National Health and Family Planning Commission to examine food safety before they can be used in food production and operation[90]. In addition, the approach declares that genetically modified food, healthy food, and new varieties of food additives are not the raw material of novel food[90]. There is no explicit provision for allergenicity assessment of novel food ingredients, although they need an examination of food safety[90]. Moreover, there is no mandatory requirement for an allergenicity assessment of food (whether or not novel food ingredients are used for production) in the current legislation[90].

Regulation in Singapore

In September 2022, the Singapore Food Agency (SFA) released its latest version of the Requirements for Safety Assessment of Novel Foods and Novel Food Ingredients, which defined novel foods as foods or ingredients with no safe use history and synthetic compounds that are chemically identical to naturally occurring compounds[91]. The document stated that the weight-of-evidence approach would apply to determining the risk of allergenicity in novel foods, which means the source of protein, amino acid sequence comparisons, *in vitro* degradation studies, and specific serum screening and cell/in vivo based assays would also depend on the specific situation[91].

Regulation with FAO/WHO

There are no substantive legal provisions for new food. The Codex Alimentarius Commission (CAC) just noticed the FAO/WHO paper on emerging issues affecting agri-food systems with relevance to food safety and the quality of new food sources and production systems in 2021[3]. Between 2021 to 2022, FAO has three reports on food safety aspects of edible insects, seaweed, and cell-based food ('Looking at edible insects from a food safety perspective. Challenges and opportunities for the sector', 'Report of the expert meeting on food safety for seaweed: current status and future perspectives' 'Food safety aspects of cell-based food'). These reports show food traceability and allergen labeling management are the core of avoiding potential allergenic risks in food.

Conclusions

Novel foods can cause allergies in many ways. Firstly, new technology innovations can enrich the nutrients in food, and the nutrient levels may exceed the threshold for causing food allergy[62,92]. Technological innovations can also alter the structure of known food nutrients, exposing allergen epitopes to cause food allergies[93]. Some new resource foods introduced multiple new nutrient profiles. At the same time, unknown allergens also could be introduced that may cause unexpected allergies[94]. Moreover, novel foods may also directly or indirectly alter the body's immune function and affect the body's tolerance to allergens[95].

Nowadays, we rely on information on known allergens in novel foods to manage allergy risks. The regulations for novel foods worldwide are often used as reference points for assessing whether novel foods are safe to consume. Many countries have implemented risk management for novel foods containing known allergens from application to consumption, such as legislation, establishing guidelines or legal frameworks, and establishing allergen databases.

Food traceability technologies are emerging approaches to improving food allergen management[3,24]. To trace allergens in foods' raw materials, the producer and/or previous handlers in the supply chain and by the assurance quality system method. But allergy risk assessment strategies focus on known allergens in novel foods. The developed methods for allergenic risk assessment of novel foods are based on known allergen epitopes. However, in addition to the identified allergens, there

are still unknown allergens in novel foods, and any other factors that cause allergies will also affect the body's tolerance to allergens. It may not be safe or reliable to rely solely on physiological reactions caused by double-blind prick testing for potential risk assessment. Reasonably, there is still a long way to go to establish a methodology for the allergenic assessment of novel foods. Controlling novel food allergy risk sounds like fantasy since food allergen risk management lags behind methodology studies.

Acknowledgments

Central Government Guide Local Special Fund Project for Scientific and Technological Development of Jiangxi Province (20221ZDD02001).

Conflict of interest

The authors declare that they have no conflict of interest.

Dates

Received 1 February 2023; Accepted 28 April 2023; Published online 30 May 2023

References

1. Willett W, Rockström J, Loken B, Springmann M, Lang T, et al. 2019. Food in the Anthropocene: the EAT-Lancet Commission on healthy diets from sustainable food systems. *The Lancet* 393:447–92
2. Anoop AA, Pillai PKS, Nickerson M, Ragavan KV. 2023. Plant leaf proteins for food applications: Opportunities and challenges. *Comprehensive Reviews in Food Science and Food Safety* 22:473–501
3. Secretariat, Codex Alimentarius Commission, Joint FAO/WHO Food Standards Programme. 2022. *Request for Information on New Food Sources and production systems; Need for Codex guidance and attention to inform the CCEXEC sub-committee on working on this topic. CL 2022/06/OCS-CCEXEC*. USA: FAO and WHO. www.fao.org/fao-who-codexalimentarius/sh-proxy/pt/?lnk=1&url=https%253A%252F%252Fworkspace.fao.org%252Fsites%252Fcodex%252FCircular%252520Letters%252FCL%2525202022-06%252Fcl22_06e.pdf
4. Vanga SK, Singh A, Raghavan V. 2017. Review of conventional and novel food processing methods on food allergens. *Critical Reviews in Food Science Nutrition* 57:2077–94
5. Tuorila H, Hartmann C. 2020. Consumer responses to novel and unfamiliar foods. *Current Opinion in Food Science* 33:1–8
6. Hendrich S. 2016. Novel Foods. In *Encyclopedia of Food and Health. Reference Module in Food Science*, eds. Caballero B, Finglas PM, Toldrá F. Oxford, UK: Academic Press. pp. 79–83. https://doi.org/10.1016/B978-0-12-384947-2.00486-4
7. Motoki K, Park J, Spence C, Velasco C. 2022. Contextual acceptance of novel and unfamiliar foods: Insects, cultured meat, plant-based meat alternatives, and 3D printed foods. *Food Quality and Preference* 96:104368
8. Gallo M, Ferrara L, Calogero A, Montesano D, Naviglio D. 2020. Relationships between food and diseases: What to know to ensure food safety. *Food Research International* 137:109414
9. Jones SM, Burks AW. 2017. Food allergy. *The New England Journal of Medicine* 377:1168–76
10. Cianferoni A. 2021. Non-IgE-mediated anaphylaxis. *The Journal of Allergy and Clinical Immunology* 147:1123–31
11. Liu C, Sathe SK. 2018. Food allergen epitope mapping. *Journal of Agricultural and Food Chemistry* 66:7238–48
12. Nowak-Węgrzyn A, Katz Y, Mehr SS, Koletzko S. 2015. Non–IgE-mediated gastrointestinal food allergy. *The Journal of Allergy and Clinical Immunology* 135:1114–24
13. Simon D, Cianferoni A, Spergel JM, Aceves S, Holbreich M, et al. 2016. Eosinophilic esophagitis is characterized by a non-IgE-mediated food hypersensitivity. *Allergy* 71:611–20
14. Sampath V, Sindher SB, Alvarez Pinzon AM, Nadeau KC. 2020. Can food allergy be cured? What are the future prospects? *Allergy* 75:1316–26
15. Keet CA, Berin MC. 2022. The year in food allergy. *The Journal of Allergy and clinical immunology* 149:867–73
16. Skypala IJ, McKenzie R. 2019. Nutritional issues in food allergy. *Clinical Reviews in Allergy & Immunology* 57:166–78
17. Bhanegaonkar A, Horodniceanu EG, Ji X, Detzel P, Boguniewicz M, et al. 2015. Economic burden of atopic dermatitis in High-Risk infants receiving cow's milk or partially hydrolyzed 100% Whey-based formula. *The Journal of Pediatrics* 166:1145–51
18. Giacalone D, Jaeger SR. 2023. Consumer acceptance of novel sustainable food technologies: A multi-country survey. *Journal of Cleaner Production* 408:137119
19. Mazac R, Järviö N, Tuomisto HL. 2023. Environmental and nutritional Life Cycle Assessment of novel foods in meals as transformative food for the future. *The Science of The Total Environment* 876:162796
20. Castan L, Bøgh KL, Maryniak NZ, Epstein MM, Kazemi S, et al. 2020. Overview of *in vivo* and *ex vivo* endpoints in murine food allergy models: Suitable for evaluation of the sensitizing capacity of novel proteins? *Allergy* 75:289–301
21. Ballegaard ASR, Bøgh KL. 2023. Intestinal protein uptake and IgE-mediated food allergy. *Food Research International* 163:112150
22. Fernandez A, Mills ENC, Koning F, Moreno FJ. 2019. Safety Assessment of immune-mediated adverse reactions to novel food proteins. *Trends in Biotechnology* 37:796–800
23. Fernandez A, Mills ENC, Koning F, Moreno FJ. 2021. Allergenicity assessment of novel food proteins: What Should Be Improved? *Trends in Biotechnology* 39:4–8
24. Jia L, Evans S. 2021. Improving food allergen management in food manufacturing: An incentive-based approach. *Food Control* 129:102846
25. Taylor SL, Godefroy SB. 2023. Novel foods and ingredients: laws and regulations in USA and Canada. In *Sustainable Food Science - A Comprehensive Approach*, ed. Ferranti P. Netherlands: Elsevier. pp. 59–64. https://doi.org/10.1016/B978-0-12-823960-5.00068-8
26. Brooke-Taylor S, Grinter K. 2023. Novel food and ingredients: laws and regulations Australia and New Zealand. In *Sustainable Food Science - A Comprehensive Approach*, ed. Ferranti P. Netherlands: Elsevier. pp. 75–85. https://doi.org/10.1016/B978-0-12-823960-5.00040-8
27. Crevel R. 2023. Novel foods and ingredients: laws and regulations Europe. In *Sustainable Food Science - A Comprehensive Approach*, ed. Ferranti P. Netherlands: Elsevier. pp. 65–74. https://doi.org/-10.1016/B978-0-12-823960-5.00047-0
28. Mathur M, Kumar A, Ariyadasa TU, Malik A. 2021. Yeast assisted algal flocculation for enhancing nutraceutical potential of *Chlorella pyrenoidosa*. *Bioresource Technology* 340:125670
29. Rathod G, Amamcharla JK. 2021. Process development for a novel milk protein concentrate with whey proteins as fibrils. *Journal of Dairy Science* 104:4094–107
30. Cabanillas B, Novak N. 2019. Effects of daily food processing on allergenicity. *Critical Reviews in Food Science and Nutrition* 59:31–42
31. Lozano-Ojalvo D, Berin C, Tordesillas L. 2019. Immune basis of allergic reactions to food. *Journal of Investigational Allergology and Clinical Immunology* 29:1–14
32. Kopko C, Garthoff JA, Zhou K, Meunier L, O'Sullivan AJ, et al. 2022. Are alternative proteins increasing food allergies? Trends, drivers and future perspectives *Trends in Food Science & Technology* 129:126–33

33. Fasolin LH, Pereira RN, Pinheiro AC, Martins JT, Andrade CCP, et al. 2019. Emergent food proteins - Towards sustainability, health and innovation. *Food Research International* 125:108586
34. Zhang J, Liu X, Wang Z, Zhang H, Gao J, et al. 2022. Potential Allergenicity response to *Moringa oleifera* leaf proteins in BALB/c mice. *Nutrients* 14:4700
35. Meng X, Zeng Z, Gao J, Tong P, Wu Y, et al. 2020. Conformational changes in bovine α-lactalbumin and β-lactoglobulin evoked by interaction with C18 unsaturated fatty acids provide insights into increased allergic potential. *Food & Function* 11:9240–51
36. Kabasser S, Hafner C, Chinthrajah S, Sindher SB, Kumar D, et al. 2021. Identification of Pru du 6 as a potential marker allergen for almond allergy. *Allergy* 76:1463–72
37. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, Castenmiller J, et al. 2022. Safety of 3-fucosyllactose (3-FL) produced by a derivative strain of *Escherichia coli BL21* (DE3) as a Novel Food pursuant to Regulation (EU) 2015/2283. *EFSA Journal* 20:e07329
38. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, Castenmiller J, et al. 2022. Safety of lacto-N-tetraose (LNT) produced by derivative strains of *Escherichia coli* BL21 (DE3) as a Novel Food pursuant to Regulation (EU) 2015/2283. *EFSA Journal* 20:e07242
39. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, Castenmiller J, et al. 2022. Safety of 3′-sialyl lactose (3'-SL) sodium salt produced by derivative strains of *Escherichia coli* BL21 (DE3) as a Novel Food pursuant to Regulation (EU) 2015/2283. *EFSA Journal* 20:e07331
40. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA), Turck D, Bohn T, Castenmiller J, et al. 2022. Safety of 6′-sialyl lactose (6'-SL) sodium salt produced by derivative strains of *Escherichia coli* BL21 (DE3) as a novel food pursuant to Regulation (EU) 2015/2283. *EFSA Journal* 20:e07645
41. EFSA Panel on Nutrition, Novel Foods and Food Allergens (NDA)Turck D, Bohn T, Castenmiller J, et al. 2022. Safety of 2'-fucosyllactose (2'-FL) produced by a derivative strain (APC199) of *Corynebacterium glutamicum* ATCC 13032 as a novel food pursuant to Regulation (EU) 2015/2283. *EFSA Journal* 20:e07647
42. Zhang Q, Li L, Lan Q, Li M, Wu D, et al. 2019. Protein glycosylation: a promising way to modify the functional properties and extend the application in food system. *Critical Reviews in Food Science and Nutrition* 59:2506–33
43. Fayaz G, Soleimanian Y, Mhamadi M, Turgeon SL, Khalloufi S. 2022. The applications of conventional and innovative mechanical technologies to tailor structural and functional features of dietary fibers from plant wastes: A review. *Comprehensive Reviews in Food Science and Food Safety* 21:2149–99
44. Prestes Fallavena L, Poerner Rodrigues N, Damasceno Ferreira Marczak L, Domeneghini Mercali G. 2022. Formation of advanced glycation end products by novel food processing technologies: A review. *Food Chemistry* 393:133338
45. Ho I, Peterson A, Madden J, Huang E, Amin S, et al. 2022. Will it cricket? product development and evaluation of cricket (*Acheta domesticus*) powder replacement in sausage, pasta, and brownies *Foods* 11:3128
46. Özcan E, Sun J, Rowley DC, Sela DA. 2017. A human gut commensal ferments cranberry carbohydrates to produce formate. *Applied and Environmental Microbiology* 83:e01097–17
47. Platts-Mills TA, Hilger C, Jappe U, van Hage M, Gadermaier G, et al. 2021. Carbohydrate epitopes currently recognized as targets for IgE antibodies. *Allergy* 76:2383–94
48. Apostolovic D, Rodrigues R, Thomas P, Starkhammar M, Hamsten C, et al. 2018. Immunoprofile of α-Gal- and B-antigen-specific responses differentiates red meat-allergic patients from healthy individuals. *Allergy* 73:1525–31
49. Apostolovic D, Tran TAT, Sánchez-Vidaurre S, Cirkovic Velickovic T, Starkhammar M, et al. 2015. Red meat allergic patients have a selective IgE response to the α-Gal glycan. *Allergy* 70:1497–500
50. Wilson JM, Schuyler AJ, Workman L, Gupta M, James HR, et al. 2019. Investigation into the α-Gal Syndrome: Characteristics of 261 Children and Adults Reporting Red Meat Allergy. *The Journal of Allergy and Clinical Immunology. In practice* 7:2348–58
51. Nkurunungi G, Mpairwe H, Versteeg SA, van Diepen A, Nassuuna J, et al. 2021. Cross-reactive carbohydrate determinant-specific IgE obscures true atopy and exhibits α-1,3-fucose epitope-specific inverse associations with asthma. *Allergy* 76:233–46
52. Escalante-Aburto A, Trujillo-de Santiago G, Álvarez MM, Chuck-Hernández C. 2021. Advances and prospective applications of 3D food printing for health improvement and personalized nutrition. *Comprehensive Reviews in Food Science and Food Safety* 20:5722–41
53. Prendeville H, Lynch L. 2022. Diet, lipids, and antitumor immunity. *Cellular & Molecular Immunology* 19:432–44
54. Wit M, Trujillo-Viera J, Strohmeyer A, Klingenspor M, Hankir M, et al. 2022. When fat meets the gut-focus on intestinal lipid handling in metabolic health and disease. *EMBO Molecular Medicine* 14:e14742
55. Sun T, Wang X, Cong P, Xu J, Xue C. 2020. Mass spectrometry-based lipidomics in food science and nutritional health: A comprehensive review. *Comprehensive Reviews in Food Science and Food Safety* 19:2530–58
56. López-Fandiño R. 2020. Role of dietary lipids in food allergy. *Critical Reviews in Food Science and Nutrition* 60:1797–814
57. Song JW, Liu YS, Guo YR, Zhong WX, Guo YP, et al. 2022. Nano-liposomes double loaded with curcumin and tetrandrine: preparation, characterization, hepatotoxicity and anti-tumor effects. *International Journal of Molecular Sciences* 23:6858
58. Yoshioka Y, Kuroda E, Hirai T, Tsutsumi Y, Ishii KJ. 2017. Allergic responses induced by the immunomodulatory effects of nanomaterials upon skin exposure. *Frontiers in Immunology* 8:169
59. Hils M, Wölbing F, Hilger C, Fischer J, Hoffard N, et al. 2020. The history of carbohydrates in Type I Allergy. *Frontiers in immunology* 11:586924
60. Meng X, Li X, Wang X, Gao J, Yang H, et al. 2016. Potential allergenicity response to structural modification of irradiated bovine α-lactalbumin. *Food Function* 7:3102–10
61. Graham F, Fiocchi A. 2022. The importance of threshold dose-distribution data for priority allergens and the need for future studies. *Allergy* 77:2886–87
62. Valluzzi RL, Riccardi C, Arasi S, Piscitelli AL, Calandrelli V, et al. 2022. Cow's milk and egg protein threshold dose distributions in children tolerant to beef, baked milk, and baked egg. *Allergy* 77:3052–60
63. Jimenez-Saiz R, Martos G, Carrillo W, Lopez-Fandino R, Molina E. 2011. Susceptibility of lysozyme to in-vitro digestion and immunoreactivity of its digests. *Food Chemistry* 127:1719–26
64. Li J, Wang Y, Tang L, de Villiers WJ, Cohen D, et al. 2013. Dietary medium-chain triglycerides promote oral allergic sensitization and orally induced anaphylaxis to peanut protein in mice. *The Journal of Allergy and Clinical Immunology* 131:442–50
65. Khodoun MV, Tomar S, Tocker JE, Wang YH, Finkelman FD. 2018. Prevention of food allergy development and suppression of established food allergy by neutralization of thymic stromal lymphopoietin, IL-25, and IL-33. *The Journal of Allergy and Clinical Immunology* 141:171–179.E1
66. Bublin M, Eiwegger T, Breiteneder H. 2014. Do lipids influence the allergic sensitization process? *The Journal of Allergy and Clinical Immunology* 134:521–29
67. Remington B, Broekman HCH, Blom WM, Capt A, Crevel RWR, et al. 2018. Approaches to assess IgE mediated allergy risks (sensitization and cross-reactivity) from new or modified dietary proteins. *Food and Chemical Toxicology* 112:97–107

68. Kruizinga AG, Briggs D, Crevel RWR, Knulst AC, van den Bosch LM, Houben GF. 2008. Probabilistic risk assessment model for allergens in food: sensitivity analysis of the minimum eliciting dose and food consumption. *Food and Chemical Toxicology* 46:1437–43
69. Spanjersberg MQI, Knulst AC, Kruizinga AG, Van Duijn G, Houben GF. 2010. Concentrations of undeclared allergens in food products can reach levels that are relevant for public health. *Food Additives and Contaminants Part A* 27:169–74
70. Spanjersberg MQI, Kruizinga AG, Rennen MAJ, Houben GF. 2007. Risk assessment and food allergy: the probabilistic model applied to allergens. *Food And Chemical Toxicology* 45:49–54
71. EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA), Turck D, Bresson JL, Burlingame B, et al. 2016. Guidance on preparing and presenting an application for authorisation of a novel food in the context of Regulation (EU) 2015/2283. *EFSA Journal* 14:e04594
72. Verhoeckx K, Broekman H, Knulst A, Houben G. 2016. Allergenicity assessment strategy for novel food proteins and protein sources. *Regulatory Toxicology and Pharmacology* 79:118–24
73. Mazzucchelli G, Holzhauser T, Cirkovic Velickovic T, Diaz-Perales A, Molina E, et al. 2018. Current (Food) Allergenic Risk Assessment: Is It Fit for Novel Foods? Status Quo and Identification of Gaps *Molecular Nutrition & Food Research* 62:1700278
74. Monaci L, De Angelis E, Montemurro N, Pilolli R. 2018. Comprehensive overview and recent advances in proteomics MS based methods for food allergens analysis. *TrAC Trends in Analytical Chemistry* 106:21–36
75. Gavage M, Van Vlierberghe K, Van Poucke C, et al. 2020. Comparative study of concatemer efficiency as an isotope-labelled internal standard for allergen quantification. *Food Chemistry* 332:127413
76. Project T. 2019. Detection and quantification of allergens in food and minimum eliciting doses in food allergic individuals. www.ispacnr.it/thrall-project
77. Pali-Schöll I, Verhoeckx K, Mafra I, Bavaro SL, Clare Mills EN, et al. 2019. Allergenic and novel food proteins: State of the art and challenges in the allergenicity assessment. *Trends in Food Science & Technology* 84:45–48
78. Hosu O, Selvolini G, Marrazza G. 2018. Recent advances of immunosensors for detecting food allergens. *Current Opinion in Electrochemistry* 10:149–56
79. Jeong JY, Kim SO, Bang S, Choi Y, Shin J, et al. 2023. Adaptive biosensing platform using immune cell-based nanovesicles for food allergen detection. *Biosensors and Bioelectronics* 222:114914
80. Finkelman FD. 2007. Anaphylaxis: lessons from mouse models. *The Journal of Allergy and Clinical Immunology* 120:506–15
81. Wang C, Wang Y, Liu G, Fu L. 2020. Food allergomics based on high-throughput and bioinformatics technologies. *Food Research International* 130:108942
82. Radauer C, Breiteneder H. 2019. Allergen databases - A critical evaluation. *Allergy* 74:2057–60
83. D'Auria G, Nitride C, Nicolai MA, Mamone G, Montesano D, et al. 2023. Identification of allergen encoding sequences in a novel food ingredient from *Moringa oleifera* leaves. *Food Chemistry* 401:134185
84. Brusic V, Petrovsky N. 2003. Bioinformatics for characterisation of allergens, allergenicity and allergic crossreactivity. *Trends in Immunology* 24:225–28
85. Pisanello D, Caruso G. 2018. EU regulation on novel foods. In *Novel Foods in the European Union*. Cham: Springer International Press. pp. 1–29. https://doi.org/10.1007/978-3-319-93620-8_1
86. Vapnek J, Purnhagen K, Hillel B. 2021. Regulatory and Legislative Framework for Novel Foods. In *Food Formulation: Novel Ingredients and Processing Techniques*, eds. Pathania S, Tiwari BK. Vol. 14. UK: John Wiley & Sons Ltd Press. pp. 285–308 https://doi.org/10.1002/9781119614760.ch14
87. Government of Canada. 2022. Guidelines for the Safety Assessment of Novel Foods. www.canada.ca/en/health-canada/services/food-nutrition/legislation-guidelines/guidance-documents/guidelines-safety-assessment-novel-foods-derived-plants-microorganisms/guidelines-safety-assessment-novel-foods-2006.html
88. Food Standards Australia New Zealand. 2022. Regulation of novel foods. www.foodstandards.gov.au/industry/novel/Pages/default.aspx
89. Government Australia New Zealand. 2017. Australia New Zealand Food Standards Code – Standard 1.5.1 – Novel Foods. www.legislation.gov.au/Details/F2017C00324
90. National Health Commission of the People's Republic of China. 2013. Administrative Measures for Safety Review of New Food Raw Materials (NHFPC Order No. 1). www.nhc.gov.cn/fzs/s3576/201808/b6894ec987b64af3ae75f5140130c869.shtml
91. Sigapore Food Agency. 2022. Requirements for Safety Assessment of Novel Foods and Novel Food Ingredients. www.sfa.gov.sg/docs/default-source/food-import-and-export/Requirements-on-safety-assessment-of-novel-foods_26Sep.pdf
92. Bindslev-Jensen C, Briggs D, Osterballe M. 2002. Can we determine a threshold level for allergenic foods by statistical analysis of published data in the literature? *Allergy* 57:741–46
93. Zhang Y, Wu Z, Li K, Li X, Yang A, et al. 2019. Allergenicity assessment on thermally processed peanut influenced by extraction and assessment methods. *Food Chemistry* 281:130–39
94. van Putten MC, Frewer LJ, Gilissen LJWJ, Gremmen B, Peijnenburg AACM, Wichers HJ. 2006. Novel foods and food allergies: A review of the issues. *Trends in Food Science & Technology* 17:289–99
95. Yamashita H, Matsuhara H, Miotani S, Sako Y, Matsui T, et al. 2017. Artificial sweeteners and mixture of food additives cause to break oral tolerance and induce food allergy in murine oral tolerance model for food allergy. *Clinical & Experimental Allergy* 47:1204–13