IJBPAS, April, 2025, 14(4): 1799-1811

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

NEW STEPS REGARDING EVALUATING PUBLIC HEALTH IMPORTANCE OF ADDITIONAL FOOD ALLERGENS-FDA

SANA P[1], JOSH V[2*], DR ABHISHEK B V[3]

1: M Pharm Department of Pharmaceutics & Regulatory Affairs, Sri Adichunchanagiri College of Pharmacy, B G Nagara, Karnataka, India

2: Professor, Department of Pharmaceutics & Regulatory Affairs, Sri Adichunchanagiri College of Pharmacy, B G Nagara, Karnataka, India

3: Assistant Professor, Department of Pharmaceutics & Regulatory Affairs, Sri Adichunchanagiri College of Pharmacy, B G Nagara, Karnataka, India

***Corresponding Author: Dr. Vedamurthy Joshi: E Mail: vedamurthyjoshi@gmail.com**

Received 16th Nov. 2023; Revised 18th Dec. 2023; Accepted 27th May 2024; Available online 1st March 2025

https://doi.org/10.31032/IJBPAS/2025/14.3.8851

ABSTRACT

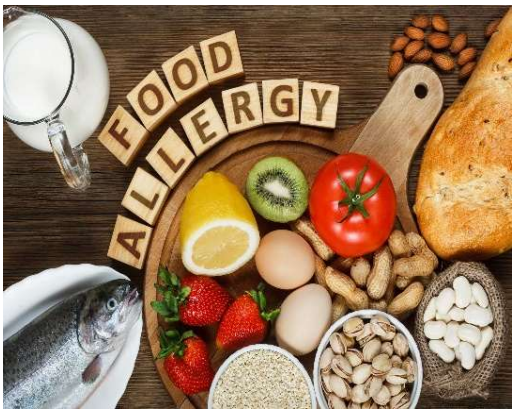
Food safety regulators are beginning to recognise food allergies as a public health issue. World Health Organisation (WHO) created a list of the foods that lead to the most allergic reactions. In order to detect and manage allergy concerns in food, the FDA offers guidelines to the food industry, consumers, and other interested parties. More than 160 foods are known to cause food allergy reactions, with the most common allergens now being milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. Sesame is the ninth significant food allergy as of January. The majority of current guidelines are focused on IgE-mediated food allergies, capable of producing anaphylaxis.

Primary goal is to provide a systematic roadmap for evaluating the public health importance of novel allergens. By merging clinical data, severity, exposure assessment and risk management considerations. For the sake of public health, regulatory knowledge and guidelines for recognising foods containing allergens are essential. To assist in determining whether allergic foods are of sufficient public health concern to be included in allergen lists. Clinical considerations (diagnosis, allergen potency, intensity of reactions), population aspects (prevalence, exposure), and moderating factors (food processing) are some of the criteria. Data supporting these criteria are weighted in the framework based on quality using a ranking established from evidence-based medicine.

Keywords: FDA, Food allergies, public health, FALCPA, FASTER, WHO, Guidelines

INTRODUCTION:

Food safety regulators are beginning to recognise food allergies as a public health issue. The World Health Organisation (WHO) created a list of the food s that lead to the most allergic reactions, however there was a dearth of information at the time. Since that time, a number of confirmed allergy reactions to a variety of allergenic foods have been recorded. The Codex list is the principal list used today for food allergen labelling throughout the world. The inclusion of allergic foods on municipal labelling lists does not adhere to a standard risk assessment and risk management decision-making process, which causes misunderstandings and practical difficulties **[1]**.



Food allergies are brought on by the immune system's reaction to proteins, which are typically safe food ingredients. Food allergies can result in a vast range of symptoms. The gastrointestinal tract (stomach aches, vomiting, or diarrhoea), the skin (hives, rashes, or dermatitis), and the airways (wheezing or breathing difficulties) are the most typical places for allergic symptoms to manifest **[2]**. It is extremely rare to experience anaphylaxis or other severe systemic responses. Regulatory efforts are concentrated on IgE-mediated food allergy since it generates the most severe (anaphylactic) symptoms and is the most common and simple to detect type of food allergy, even though food-allergic reactions appear to be linked to a number of pathways. Several foods have been connected to allergy responses in sensitive people **[3]**.

Food allergies and other food hypersensitivities affect millions of Americans as well as their families. A wide range of symptoms, from mild ones like hives and lip swelling to catastrophic ones like anaphylaxis, which can result in major breathing difficulties and shock, can be brought on by food allergies.

In order to protect people with food allergies and other food hypersensitivities, the FDA enforces rules requiring businesses to disclose ingredients on packaged foods and The main objective of the article is to describe the process of evaluation of **public health importance** for food allergens and various regulations described in the US regulations.

Allergens in food, and its detection is described in the FDA guidelines for food industry, consumers, and other interested parties. The FDA also conducts inspections and sampling to ensure that major food allergens are accurately labelled on products, to determine whether food facilities have safeguards in place to prevent allergen cross-contact.

More than 160 foods are known to cause food allergy reactions, with the most common allergens now being milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans. Sesame is the ninth significant food allergy as of January 1, 2023 **[4]**.

“The director of the Centre for Food Safety and Applied Nutrition, Susan Mayne, Ph.D., claims that "the nine major food allergens do not currently represent all foods nationwide that people are allergic to or that cause food hypersensitivities." "The FDA is working to evaluate new information about other unlisted food allergens that can cause serious reactions in a consistent and transparent manner, which can inform potential future actions to help better protect the health of consumers," according to the draught guidance - Director of the Centre for Food Safety and Applied Nutrition, claims that "the nine major food allergens do not currently represent all foods nationwide that people are allergic to or that cause food hypersensitivities. The FDA is attempting to assess newly available evidence with the use of its drafted advice.”

beverages. For certain foods or chemicals that cause allergies or other hypersensitivity reactions, there are additional, particular labelling requirements.

Figure 1: Major Food Allergens

The majority of current guidelines are focused on IgE-mediated food allergies, which are thought to be the most severe and instantaneously lethal food allergies capable of producing anaphylaxis. In all nine instances, the nine typical food allergens result in IgE-mediated responses. The FDA's general procedure for determining

the seriousness of a food allergy to a chemical that is not on its list of prohibited foods is outlined in the following guideline. It discusses important aspects including prevalence, severity, and allergenic potency that the FDA plans to take into account when making decisions, as well as the studies showing how the chemical is related to IgE-mediated food allergies. The procedures used by the FDA to find and assess the relevant body of information to assess its significance for a wider.

The Food Allergen Labelling and Consumer Protection Act (FALCPA), enacted by Congress in August 2004, was officially signed into law. The eight major food allergens at the time—milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybeans—were the main causes of severe food responses in the U.S. and accounted for 90% of IgE-mediated food allergies. Sesame was ranked as the 9th most prevalent food allergy in the US after the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act was passed on April 23, 2021. The new rule became effective on January 1st, 2023. Sesame will be subject to all FDA rules, including those that deal with labelling and manufacturing, as of January 1, 2023 **[5]**.

Labelling

The Food and Drug Administration (FDA) implements the Food Allergen Labelling and Consumer Protection Act of 2004 (the Act) to help American consumers avoid the health risks associated with food allergies. The FDA is in charge of overseeing all goods, including food, with the exception of poultry, catfish, most meats, some egg products, and most alcoholic beverages, which are controlled by other federal agencies. Labels that adhere to the Act are required for all products that fall under FDA regulation, which is applicable to all products.

Inspections

The FDA's "Current Good Manufacturing Practises, Hazard Analysis, and Risk-Based Preventive Controls for Human Food" rule (CGMP & PC rule, 21 CFR part 117) defines rules for establishments that produce, prepare, pack, or store human food. The CGMP & PC regulation establishes requirements for allergy preventative controls in order to avoid cross-contact between allergens during production and packaging as well as to prevent unreported allergens. In accordance with the relevant standards of 21 CFR part 117, the FDA inspects food manufacturers to ascertain if allergen cross-contact has been limited or prevented and whether a food facility has the necessary controls for allergen labelling.

Monitoring

The FDA keeps track of data about substances, food hypersensitivities (including gluten), and complaints regarding unfavourable food reactions. Through the

Reportable Food Registry, the FDA also receives information from the industry on unreported allergies.

Testing

The FDA conducts repeated surveys and sampling assignments to gather information on particular foods. The FDA conducts ELISA testing, in which antibodies bind to specific allergens, to determine whether there are any allergens in food. The FDA uses two different ELISA kits to evaluate food samples before certifying the results. Other techniques for testing for allergies include mass spectrometry and DNA-based polymerase chain reactions **[4]**.

Table 1: Guidance Document:[6]

SL No.	Guidance Document	Issued Date
01	Draft compliance policy guide sec 555.250: Major Food Allergen Labelling and Cross-contact. The purpose of this draft compliance policy guide is to provide guidance for FDA staff on the FDA's enforcement policy regarding major food allergen labelling and cross-contact	May 2023
02	Letter to Industry: Food Safety Risks of Transferring Genes for Proteins that are Food Allergens to New Plant Varieties Used for Food	April 2023
03	Draft Guidance for FDA Staff and Stakeholders: Evaluating the Public Health Importance of Food Allergens Other Than the Major Food Allergens Listed in the Federal Food, Drug, and Cosmetic Act	April 2022
04	The FDA Food Safety Modernization Act (FSMA): DRAFT Guidance for Industry: Hazard Analysis and Risk-Based Preventive Controls for Human Food	August 2017

DISCUSSIONS:

Risk assessment considerations for food allergy The four steps that make up the conventional breakdown of the risk assessment process are hazard identification, hazard characterisation, exposure assessment, and risk characterisation. When considering the significance of food allergies for public health, it is important to consider how easily a bad effect may be avoided by an individual as well as whether or not societal safeguards are required or the best course of action to prevent unfavourable outcomes. This article describes how to evaluate the scientific literature on food allergies from the perspective of public health and offers a framework for decision-making as a risk management tool. The framework needs to be globally applicable and suitable for risk managers in both corporate and regulatory entities. This article describes how to evaluate the scientific literature on food allergies from the perspective of public health and offers a framework for

decision-making as a risk management tool. Risk managers working for both regulatory institutions and the private sector should be able to use the framework.

Table 2: Examples of evidence from studies of food allergy in relation to criteria employed in Evidence-Based Medicine to assess strength of evidence

Level of evidence	Type	Examples
1a	Systematic review of controlled trial	Systematic review of 1b DBPCFC[a] studies
1b	Single controlled trial (with narrow confidence interval)	DBPCFC studies in well-characterised patients, with defined doses of specific food
2a	Systematic review of cohort studies	Systematic review of good quality case series
2b	Individual cohort study	Case series of documented reactions to suspected food, confirmed by DBPCFC, and IgE antibodies
2c	NA	As above, but not confirmed by DBPCFC
3a	Systematic review of case-control studies	Case reports confirmed by specific IgE to suspected food, but not DBPCFC
3b	Individual case-control study	
4	Case series (and less convincing cohort and case-control studies)	Anecdotal case reports of reactions to a food, not confirmed by IgE, but with symptoms consistent with IgE-mediated reactions
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles	Hypothesis formulated about the allergenicity of a food because of its similarity to a food the allergenicity of which has been documented

Criteria for identifying allergenic foods of public health importance

General aspects

The Food and Agriculture Organisation and Codex conducted a technical consultation in 1995 to determine the eight food categories that are most frequently linked to IgE-mediated food allergies globally. According to correctly conducted double-blind-placebo controlled food challenge (DBPCFC) trials, two crucial criteria were found to be the severity of the reactions and The first two requirements are the degree of the reaction and confirmation that a food may cause an IgE-mediated reaction. The available clinical data types are listed in allergenicity. Thresholds for eliciting doses and processing components could not be added at the time, even though they were considered to be important. **Figure 2** depicts the suggested framework and the criteria that should be considered when deciding if a food allergy is significant enough to the public health to call for risk management measures. Despite the fact that some of the links between the stated criteria are tenuous.

Verification of diagnosis and severity

Table 2, together with the weights that should be given to each one according on the quality of the data. A score system **(Table 1)** that has been modified from the criteria used

in evidence-based medicine is used to evaluate these. Further serological evidence would therefore be required to demonstrate that the reported adverse effects are IgE mediated. The clinical signs that have been noticed can be used to measure the response's strength. The occurrence of these symptoms would support the theory that the food is truly most likely to be a food allergy with significance for public health

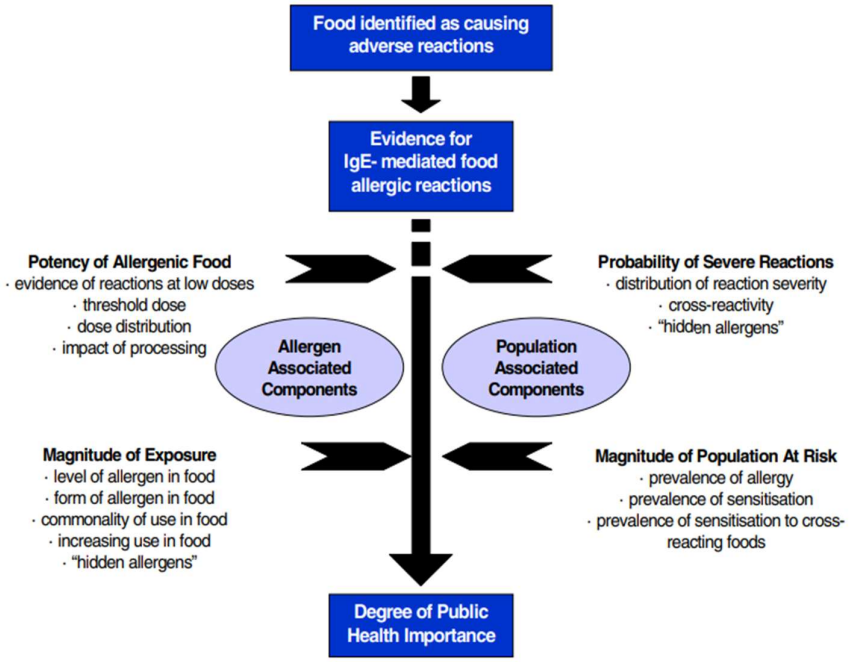


Figure 2: Framework of criteria employed to identify allergenic foods of public health importance

Table 3: Type and level (weight) of evidence of clinical data in IgE-mediated food allergy

Data supporting	Type of evidence	Level of evidence
IgE-mediated mechanism	At least two studies, in which the patient samples and food proteins are well defined, demonstrating the presence of bound IgE antibodies	1
	Serological studies showing specific IgE binding to foods/extracts	2
	Studies of small numbers of serum samples from patients who are not adequately characterise	3
Adverse reactions caused by IgE-mediated reactions	Systematic DBPCFC[a,b] studies in well-characterised patients, with defined doses of specific food and with specific bound IgE antibodies	1
	Series of patients with well-documented reactions to suspected food, confirmed by DBPCFC[a], and with IgE antibodies	2a
	As above, but not confirmed by DBPCFC[a,b]	2b
	Case reports of clinical symptoms and the presence of food-specific bound IgE antibodies, but not confirmed by DBPCFC	3
	Elimination diets leading to resolution of symptoms	4

- **Allergenicity**

Even if the majority of meals are expertly prepared, just a small percentage of their proteins truly have the capacity to cause allergies. Furthermore, proteins only include a few small, reactive amino acid molecules. For instance, those who are allergic to milk may react to many proteins or various epitopes on a single protein. As a result, various apple cultivars or fish species, for example, may contain varying quantities of allergenic proteins. Environmental factors including as growth conditions, ripeness, and storage settings might affect allergenicity. The term "allergenic potency" refers to the amount of an allergic meal needed to trigger a reaction in a person who is already sensitive to it or to make them more sensitive. This is due to the fact that risk management for common allergens places more focus on lowering the likelihood of unpleasant reactions in allergic individuals than it does on preventing allergic individuals from developing allergies. The "severity dose-response," which depicts the gradient of severity of reactions brought on by the meal, or the "frequency dose-response," which represents the population distribution of dosages that elicit or trigger a reaction, can both be used to illustrate potency.

Clinical investigations can use serial challenge tests to establish the minimal eliciting doses (MED) for certain food allergies, starting at very low doses. Finding adequate human test participants who are representative of the allergic community can be difficult, though. The eliciting dose (ED) at which 5% (ED5) or 1% (ED1) of the population would be expected to react could be computed by statistically fitting dose-distribution curves.

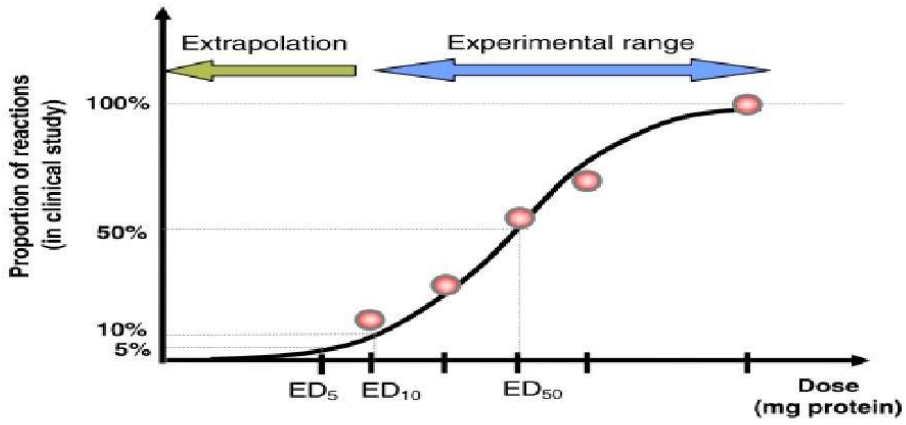


Figure 3: Illustration of the generic relationship between dose of allergenic protein and frequency of adverse reactions in clinical challenge studies. A theoretical eliciting dose (ED) can be extrapolated from the graph of experimental responses to a range of standard challenge doses

Table 4: Type and level (weight) of evidence for allergenic potency, severity of reactions and prevalence

Data supporting	Type of evidence	Level of evidence
Potency	Threshold studies with good range of doses and adequate numbers of well characterized participants, preferably multi-centre	1
	Other threshold studies	2a
	Case reports describing reactions to low doses with well-documented evidence of dose	2b
	Case reports describing reactions to low doses with documented evidence of dose	3
Severity	Systematic threshold studies demonstrating thresholds for reactions of different severity (e.g., subjective vs mild objective)	1b
	Series of patients demonstrating reactions to different doses, preferably in same individuals	2
	Case reports demonstrating reactions to different doses 3 Data from patient registers of severe reactions	3 3–4
	History of safe use	4
Prevalence	Epidemiological studies in defined populations, including verification of IgE antibodies and DBPCFC	1a
	As above but without DBPCFC	1b
	Epidemiological studies based on validated questionnaires Surveys of allergy clinic patients and other subgroups Registers of severe allergic reactions	2 3 3

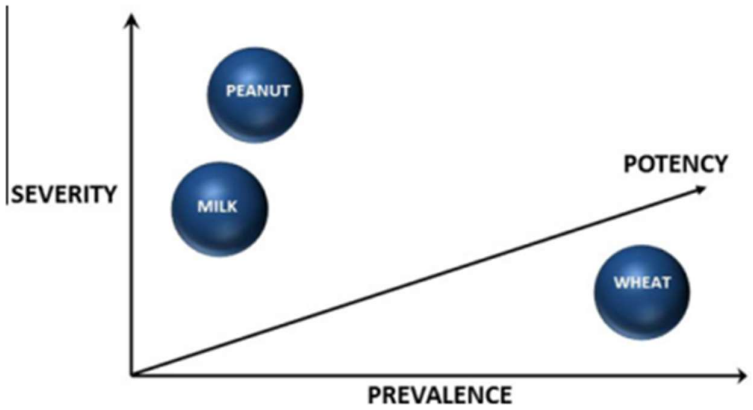


Figure 4: Diagram illustrating the potential for three-dimensional relative positioning of allergenic foods against the three key criteria of potency, severity and prevalence

The relationship between dosage and reaction strength is mostly unknown. According on a chart analysis of 538 diagnostic challenges, the majority of dosages exceeding 100 mg were linked to detrimental side effects. However, additional studies and case studies indicate that significant reactions may occur at doses considerably lower than 100 mg. Most likely, MEDs for any reaction, even any mild reactions observed in low dosage challenge experiments, will continue to be the risk assessor's best source of information.

The quantity of generated peptides and proteins in the finished product determines

its potential allergenicity. For instance, because highly refined soybean oil contains little to no protein it is generally regarded safe for people with soybean allergies. It can also be very important to consider the composition of the protein from the allergenic source. For persons with a cod-fish allergy, it has been demonstrated that gram-sized intakes of fish gelatine, a collagen-based fish product, are safe. Food processing frequently reduces the effectiveness of foods that are allergenic by denaturing, deaminating, or modifying the chemical structure of proteins, though on rare occasions this influence may even be the opposite. The folding structure may be changed to find or make new epitopes. Proteins in milk, eggs, fish, crustaceans, peanuts, and soy are just a few examples of foods whose proteins can withstand heat. When heated or processed in the digestive tract, other allergenic proteins, such those linked to pollen and found in celery and hazelnuts, become more labile **[7]**.

- **Prevalence**

The best information currently available to estimate the prevalence (number of allergic people in a population at a specific time) of a specific food allergy includes a study of the general population, clinical demonstration of adverse reactions to the allergen, preferably by DBPCFC, and clinical documentation of an IgE-mediated mechanism for the adverse reaction. When combined, these data may provide an adequate estimate of prevalence if DBPCFC data are not available but data demonstrating the presence of food-specific IgE and histories of clinical reactions to food are available. They do offer details regarding the levels and ranges of sensitivity among particular people as well as the severity of allergy reactions, and they can be used to rank allergenic foods.

In studies of representative populations, skin prick tests (SPT) and/or allergen-specific serum IgE antibodies are routinely used to determine the prevalence of sensitisation. Estimates of the prevalence may be inaccurate, though, due to the poor quality, lack of sensitivity, and occasionally even specificity of many diagnostic techniques employed in vitro and in vivo for the detection of IgE antibodies to foods. Self-reported allergy, doctor-diagnosed allergy based on clinical history, and DBPCFC and presence of IgE antibodies tests in a representative community sample can all be used to estimate the prevalence of food allergies in the general population.

Comparing self-reported food allergy prevalence to objective measurements such IgE antibody levels and provocation tests, it was found that the former was significantly higher. Even after age stratification, there was still a clear difference between the trials. The study highlights how challenging it is to

find trustworthy prevalence data that can be utilised to assess a broad range of demographics. As opposed to the 10-fold overestimations reported in early studies, new validations of telephone survey data imply that this overestimation is currently no larger than by a factor of 2 **[3]**.

- **Risk characterisation**

A population may be susceptible in a fairly wide range to any dietary allergy. The majority of people—more than 95%—are not even mildly sensitive, therefore no dose will have any negative effects on them. While the majority of allergic persons are simply moderately sensitive, a small percentage of allergic people will be severely reactive and may experience anaphylactic crises following exposure to even very low levels. Thus, sensitivity may increase in response to ailments like poorly controlled asthma, infections, stress, alcohol, some medicines, exercise, and possibly hormonal influences, but this hasn't been demonstrated. The matrix of the allergen may also have an impact on certain people's sensitivities, most likely through altering the kinetics of release from the meal. most likely through changing the kinetics of the release.

- **Exposure**

There are two main ways that consumers may unintentionally come into contact with allergens: either through components that have been purposefully introduced but are not labelled, or accidentally through activities in the supply chain. However, risk managers must also take into account accidental exposure. The majority of legislation explicitly aimed at allergens attempts to ensure that intentionally added allergens are always stated. A non-exhaustive set of exposure considerations is provided in **Table 4**. If an allergic person is exposed to more allergenic food than their personal threshold, they will react. The emphasis of the risk evaluation must be on the amount consumed on a single occasion rather than numerous exposures to low levels, which is in contrast to how it is typically done for other dietary components. They are crucial for risk management because through per capita consumption and overall consumer volume, they have an impact on the potential number of receptive individuals.

Adventitious or ‘‘hidden” exposure relates to the unexpected presence of an allergen in a food product which the individual may be unfamiliar with. For example, milk, soy, wheat or egg protein may be present in a meat sausage or casein may be used as a binder in canned fish. Additionally, novel ingredients may be substituted for a traditional one, for example, lupin and pea proteins used as soy replacers. Lupin flour has become a problem for public health issues because it is purposefully used as an

ingredient in food preparation but is not normally required to be labelled by name (EFSA, 2005). The prevalence of peanut allergy in the population exposed to inadvertent or "hidden" lupin presence in processed food raises the level of public health concern in this situation.

Table 5: Factors to consider when assessing risk of exposure to an allergenic food [7]

Use of food	Common, rare, new use
Form of allergen in food	Hydrolysed, denatured, native
Amount of protein and derived peptides present in ingredient	Analytical studies on representative samples establishing level of allergen/amount of protein or derived peptides present in ingredient. Impact of refining process
Evidence of impact of processing	Increase or decrease potency of allergen Generation of neo-allergens
'Hidden' allergen	Not easily recognisable as a constituent of the food From inadvertent cross-contact
Cross-reactivity	Allergen present in a food that cross-reacts with an allergen to which the consumer is sensitive

CONCLUSION:

Food allergy is a substantial, widely recognised public health issue. However, a variety of factors make determining and managing risk more challenging. When taken in regular proportions, allergenic foods do not affect people who are not sensitive to them, in contrast to many chemical or microbiological hazards. Numerous common and essential ingredients of a balanced diet also cause allergies. So that interventions can be targeted in the most effective way, prioritisation is required for the management of the risk posed by food allergies.

Applying standardised risk management techniques to all allergenic foods will burden society without significantly **improving public health**. Based on the application of a number of criteria, allergenic foods are necessary for public health, with the quality and strength of the supporting evidence being weighted differently for each criterion.

Indicators of an IgE-mediated adverse reaction, assessments of the frequency and severity of reactions, a meal's possible allergenicity, and the degree, pattern, and kind of exposure to the food are among the criteria. A systematic and uniform examination of the evidence would be beneficial to the conversation between risk managers and stakeholders from various geographical jurisdictions.

REFERENCES:

[1] [Internet]. [cited 2023 Aug 30]. Available from: https://ilsi.eu/wp-

content/uploads/sites/3/2016/06/2012-RTP-Chung.pdf

[2] Causes and prevention of food allergy [Internet]. U.S. Department of Health and Human Services; [cited 2023 Aug 31]. Available from: https://www.niaid.nih.gov/diseases-conditions/food-allergy-causes-prevention

[3] Author links open overlay panel J.H.M. van Bilsen a, a, b, c, d, f, *et al*. Evaluation of scientific criteria for identifying allergenic foods of public health importance [Internet]. Academic Press; 2010 [cited 2023 Aug 30]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S0273230010001510

[4] Center for Food Safety and Applied Nutrition. Food allergies [Internet]. FDA; [cited 2023 Aug 30]. Available from: https://www.fda.gov/food/food-labeling-nutrition/food-allergies

[5] Commissioner O of the. FDA takes new steps regarding evaluating public health importance of additional food allergens [Internet]. FDA; [cited 2023 Aug 30]. Available from: https://www.fda.gov/news-events/press-announcements/fda-takes-new-steps-regarding-evaluating-public-health-importance-additional-food-allergens

[6] Center for Food Safety and Applied Nutrition. Draft guidance: Evaluating public health importance of food allergens [Internet]. FDA; [cited 2023 Aug 31]. Available from: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/draft-guidance-fda-staff-and-stakeholders-evaluating-public-health-importance-food-allergens-other

[7] Author links open overlay panel. Björk Sten a, a, b, c, d, j, *et al*. Criteria for identifying allergenic foods of public health importance [Internet]. Academic Press; 2008 [cited 2023 Aug 30]. Available from: https://www.sciencedirect.com/science/article/abs/pii/S027323000800007X