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MEETING REPORT

RISK ASSESSMENT OF FOOD ALLERGENS

PART 1: REVIEW AND VALIDATION OF CODEX ALIMENTARIUS PRIORITY ALLERGEN LIST THROUGH RISK ASSESSMENT

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FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
WORLD HEALTH ORGANIZATION
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CONTRIBUTORS

EXPERTS

Joseph Baumert, Department of Food Science & Technology/Food Allergy Research & Resource Program, University of Nebraska-Lincoln, the United States of America

Simon Brooke-Taylor, Brooke-Taylor & Co Pty Ltd, Australia

Huilian Che, College of Food Science and Nutritional Engineering, China Agricultural University, China

Hongbing Chen, Sino-German Joint Research Institute; Research leader, State Key Laboratory of Food Science and Technology, Nanchang University, China

René Crevel, René Crevel Consulting Limited, the United Kingdom of Great Britain and Northern Ireland

Geert Houben, TNO Principal Scientist, Food Allergy and Immunotoxicology, the Netherlands

Lauren Jackson, Chief Process Engineering Branch, Division of Food Processing Science & Technology, Office of Food Safety, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, the United States of America

Symeon Kyriakidis, Independent Authority for Public Revenue (IAPR), General Chemical State Laboratory (GCSL) - A' Chemical Service of Athens (Public Sector), Greece

Sébastien La Vieille, Food Directorate, Heath Canada, Canada

N Alice Lee, School of Chemical Engineering, University of New South Wales, Australia

María Cristina López, Food Engineering Department San Martín National University, Argentina

Stefano Luccioli, Office of Compliance, Center for Food Safety and Applied Nutrition, US Food and Drug Administration, the United States of America

Patrick O'Mahony, Food Science & Technology Food Safety Authority of Ireland (FSAI), Ireland

Gustavo Polenta, Protein Lab of the Institute of Food Technology, Instituto Nacional de Tecnología Agropecuaria (INTA), Argentina

Bert Pöpping, FOCOS GbR, Germany

Benjamin Remington, Remington Consulting Group B.V., the Netherlands

Eva Södergren, Team Dietary Surveys & Nutrition Department for Risk Benefit Assessment, Swedish Food Agency, Sweden

Sirinrat Srikulnath, Food Quality Assurance Service Center (FQA), Institute of Food Research and Product Development (IFRPD), Kasetsart University, Thailand

Stephen Taylor, Department of Food Science & Technology University of Nebraska-Lincoln, the United States of America

Paul Turner, Paediatric Allergy & Immunology, National Heart & Lung Institute, Imperial College, the United Kingdom of Great Britain and Northern Ireland

RESOURCE PERSONS

Simon Flanagan, Mondelez International, Switzerland

Markus Lacorn, R&D Food & Feed Study Management and Validation R-Biopharm AG, Germany

Clare Mills, Molecular Allergology, School of Biological Sciences Manchester Institute of Biotechnology University of Manchester, the United Kingdom of Great Britain and Northern Ireland

Emilio Esteban, USDA Food Safety and Inspection Service, the United States of America

Kathy Twardek, Canadian Food Inspection Agency, Canada

Douglas Balentine, Office of Nutrition and Food Labeling, U.S. Food and Drug Administration, the United States of America

Verna Carolissen, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Italy

Sarah Cahill, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Italy

Lingping Zhang, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Italy

Patrick Sekitoleko, Joint FAO/WHO Food Standards Programme, Food and Agriculture Organization of the United Nations, Italy

SECRETARIAT

Markus Lipp, Food Systems and Food Safety, Food and Agriculture Organization of the United Nations, Italy

Jeffrey LeJeune, Food Systems and Food Safety, Food and Agriculture Organization of the United Nations, Italy

Vittorio Fattori, Food Systems and Food Safety, Food and Agriculture Organization of the United Nations, Italy

Kang Zhou, Food Systems and Food Safety, Food and Agriculture Organization of the United Nations, Italy

Christine Kopko, Food Systems and Food Safety, Food and Agriculture Organization of the United Nations, Italy

Haruka Igarashi, Department of Nutrition and Food Safety, World Health Organization, Switzerland

Stephan Walch, Chemisches und Veterinäruntersuchungsamt (CVUA) Karlsruhe, Germany

Carmen Diaz-Amigo, FOCOS GbR, Germany

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ABBREVIATIONS AND ACRONYMS

CAC	Codex Alimentarius Commission
CCFH	Codex Committee on Food Hygiene
CCFL	Codex Committee on Food Labelling
DBPCFC	Double-blind, placebo-controlled food challenge
EDp	Eliciting dose refers to the proportion (p) of the allergic population predicted by dose distribution modelling to react to a specified amount (dose) of total allergenic protein in a food
ED10	The eliciting dose predicted to provoke reactions in 10% of the allergic population
ED50	The eliciting dose predicted to provoke reactions in 50% of the allergic population
FAO	Food and Agriculture Organization of the United Nations
GPFH	General Principles of Food Hygiene
GSLPF	General Standard for the Labelling of Packaged Foods
ICD	International Classification of Disease
Icsa	Interval-censoring analysis
IgA	Immunoglobulin A
IgE	Immunoglobulin E
HLA	Human leukocyte antigens
JECFA	Joint FAO/WHO Expert Committee on Food Additives
LOAEL	Lowest observed adverse effect level
MED	Minimum eliciting dose
NOAEL	No observed adverse effect level
OFC	Oral food challenge
PAL	Precautionary allergen or advisory labelling
SPT	Skin prick testing
WHO	World Health Organization

DECLARATIONS OF INTERESTS

All participants completed a Declaration of Interests form in advance of the meeting. Three of the Experts declared interest in the topic under consideration. Markus Lacorn and Simon Flanagan declared significant interests connected with their employment and Clare Mills declared interests connected to investments that exceeded the FAO/WHO's threshold. It could not be excluded that the declared interests may be perceived as a potential conflict of interest. Therefore, while all three persons mentioned above had been invited to participate in the meeting, they had been excluded from the decision-making process regarding final recommendations and participated as technical resource people.

All remaining experts were not considered by FAO and WHO to have declared any interest that may be perceived as a potential conflict with regard of the objectives of the meeting.

All the declarations, together with any updates, were made known and available to all the participants at the beginning of the meeting.

All the experts participated in their individual capacities and not as representatives of their countries, governments or organizations.

EXECUTIVE SUMMARY

The first in a series of three meetings of an ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens was held from 30 November to 11 December 2020, with an additional two days, 29 January and 8 February 2021, for the report finalization and adoption of the conclusions and recommendations. The main purpose of this first meeting was to validate and, if necessary, update the list of foods and ingredients listed in section 4.2.1.4 of the General Standard for the Labelling of Packaged Foods (GSLPF) based on risk assessment. An Expert Committee, comprised of scientists, regulators, physicians, clinicians and risk assessors from academia, government and the food industry were selected to participate in the first meeting of the FAO/WHO Expert Consultation on Risk Assessment of Food Allergens. To achieve the validation of the allergen list, the Committee first identified and agreed upon the criteria for assessing additions and exclusions to the foods and ingredients listed in section 4.2.1.4 of the GSLPF. Subsequently, the Committee clarified the groupings of foods and ingredients on the list and determined whether certain foods and ingredients that are derived from the list of foods known to cause immune hypersensitivity can be exempted from mandatory declaration.

The Expert Committee determined that only foods or ingredients that cause immune-mediated hypersensitivities such as IgE-mediated food allergies and coeliac disease should be included on the list of foods and ingredients included in section 4.2.1.4 of the GSLPF. Thus, it was recommended that foods or ingredients such as lactose, sulphite, and food additives, which do not cause immune-mediated adverse reactions, will not be included in the deliberations of the committee. The Committee identified prevalence of an immune-mediated hypersensitivity to a specific food, severity (e.g. frequency or proportion of severe objective reactions to a food/ingredient such as anaphylaxis), and the potency of the food/ingredient (e.g. the amount of the total protein from the food/ingredient required to cause objective symptoms in a specified proportion) as the key criteria that should be used to establish the priority allergen list. Subgroups of the Expert Committee were established to review the literature on the prevalence, severity and potency of immune-mediated hypersensitivity to each food currently on the GSLPF list (cereals containing gluten and products of these; crustacea and products of these; eggs and egg products; fish and fish products; peanuts, soybeans and products of these; milk and milk products; and tree nuts and tree nut products), as well as other foods found on priority allergen lists established in individual countries or regions (e.g. molluscs, mustard, celery, sesame, buckwheat, lupin and others).

Based on systematic and thorough assessments which used all three criteria (prevalence, severity and potency), the Expert Committee recommended that the following should be listed as priority allergens: cereals containing gluten

(e.g. wheat and other *Triticum* species, rye and other *Secale* species, barley and other *Hordeum* species and their hybridized strains), crustacea, eggs, fish, milk, peanuts, sesame, and specific tree nuts (almond, cashew, hazelnut, pecan, pistachio and walnut). Of the cereals containing gluten, barley and rye (and cross-breeds of these cereal grains) were included on this list because they are foods that cause coeliac disease. In addition to causing coeliac disease, wheat is also responsible for food allergies.

Due to the lack of data on prevalence, severity and/or potency, or due to regional consumption of some foods, the Committee recommended that some of the allergens, such as buckwheat, celery, lupin, mustard and some tree nuts (Brazil nut, macadamia and pine nuts) should not be listed as global priority allergens but may be considered for inclusion on priority allergen lists in individual countries.

Due to a combination of low global prevalence, low allergenic potency and generally low severity of soybean allergies, soybean was not included in the list of global priority allergens. However, it may still be considered for inclusion on priority allergen lists in individual countries.

Since current dietary trends include increased consumption of plant-based foods and diets consisting of alternative protein sources, it was recommended that pulses, insects and other foods such as kiwi fruit be included in a "watch list" and evaluated for the priority allergen list when data on prevalence, severity and potency become available. Finally, the Expert Committee recommended that foods and ingredients derived from the list of foods known to cause immune-mediated hypersensitivities should be evaluated on a case-by-case basis for exemption from declaration on ingredient lists and/or on food packaging.

CHAPTER 1
INTRODUCTION

1.1. BACKGROUND

The labelling of food allergens in pre-packaged foods plays a key role in protecting food allergic individuals as no preventative clinical treatment is currently available. Although the latest developments in immunotherapy with food allergens have shown promising results, avoidance of the offending food remains the only option to prevent allergic reactions.

Allergens in food have been considered by the Codex Alimentarius Commission (CAC) on a number of occasions since 1993. In 1995, the Food and Agriculture Organization of the United Nations (FAO) organized a Technical Consultation (FAO, 1995) that resulted in the identification of eight foods or food groups causing food allergy. They were incorporated in the General Standard for the Labelling of Packaged Foods (GSLPF) in 1999 (section 4.2.1.4) (FAO and WHO, 2018a):

- cereals containing gluten, i.e. wheat, rye, barley, oats, spelt or their hybridized strains and products of these;
- crustacea and products of these;
- eggs and egg products;
- fish and fish products;
- peanuts, soybeans and products of these;
- milk and milk products (lactose included);
- tree nuts and nut products; and
- sulphite in concentrations of 10 mg/kg or more.

This list has been known informally as the "Big 8" food allergens as they are the most common and are responsible for most allergic reactions, although about 170 foods have been reportedly implicated in allergic reactions (Boyce *et al.*, 2011; Hefle, Nordlee and Taylor, 1996).

In 1999, following the FAO technical consultation, WHO convened an ad hoc Panel on Food Allergens. The Panel recommended the following criteria for the addition of foodstuffs/products to the list of the CCFL (FAO and WHO, 2000):

*Criteria for inclusion of a **foodstuff**:*

(i) the existence of a credible cause-and-effect relationship, based on a positive reaction to a double-blind placebo-controlled food challenge (DBPCFC) or unequivocal reports of a reaction with the typical features of a severe allergic or intolerance reaction;

(ii) the existence of reports of systemic reactions after exposure to the foodstuff, the reactions including atopic dermatitis, urticaria, angio-oedema, laryngeal oedema, asthma, rhinitis, abdominal pain, diarrhea, vomiting, anaphylactic shock and chronic severe malabsorption syndrome;

(iii) the existence of data on the prevalence of food allergies in children and adults, supported by appropriate clinical studies (i.e. DBPCFC) in the general population of several countries. However, the Panel noted that such information is available only for infants, from certain countries and for certain foodstuffs. The panel therefore agreed that any available data, such as the comparative prevalence of a specific food allergy in groups of patients in several countries, could be used as an alternative, preferably backed up by the results of a DBPCFC.

The list adopted by the Codex Committee on Food Labelling (CCFL) includes not only allergenic foods but also products of such foods. Because allergens are naturally occurring proteins, the Panel considered whether the definition is too broad in that it may include products that are not allergenic because they do not contain sufficient protein to elicit an allergic reaction. The available data do not, however, permit definition of the amount of allergenic protein necessary to elicit an allergic reaction.

The Panel therefore recommended that products of the allergenic foods on the list of the CCFL should always be labeled as such, unless they are on the list of products that are excluded from the requirement for labelling of the food source.

*Criteria for inclusion of a **product**:*

(i) evidence that a clinical study with a DBPCFC has confirmed that the specific product does not elicit allergic reactions in a group of patients with clinical allergy to the parent foodstuff;

(ii) submission of specifications for the product and its manufacturing process which demonstrate that the process yields a consistently safe product; and

(iii) for products implicated in coeliac disease:

- Products of rye, barley and oats would not be required to meet the criteria set out in (i) and (ii) above because IgE-mediated allergic reactions to these cereal grains are uncommon.
- Products of wheat, spelt and their hybridized strains would be required to meet the criteria set out in (i) and (ii) above.
- Products of wheat, rye, barley, oats and spelt and their hybridized strains would be required to adhere to existing specifications for gluten-free products.

The CCFL is currently reviewing provisions relevant to allergen labelling in the GSLPF as well as developing guidance on the use of precautionary allergen or advisory labelling (PAL) (FAO and WHO, 2019). The Codex Committee on Food Hygiene (CCFH) has developed a Code of Practice (CoP) on Food Allergen Management for Food Business Operators, which was adopted in 2020. This CoP provides guidance on allergen management in food production, including controls to prevent cross-contact where an allergen is inadvertently transferred from a food containing an allergen to a food that does not contain the allergen (FAO and WHO, 2020a). The General Principles of Food Hygiene (GPFH) was also updated in 2020 and includes information on the control of allergens (FAO and WHO, 2020b). The CoP is intended to complement the GPFH and the GSLPF and support industry compliance.

There have been many scientific developments in the understanding of food allergens and their management since the original drafting of the GSLPF. Thus, in response to the request from the CCFL and CCFH for scientific advice, including current evidence of consumer understanding of allergens, FAO and WHO are convening a series of expert meetings to provide scientific advice on this subject.

1.2. APPROACH

Building on the work initiated in 2020, the the request for scientific advice was divided into three main areas.

TASK 1 REVIEW AND VALIDATION OF CODEX ALIMENTARIUS PRIORITY ALLERGEN LIST THROUGH RISK ASSESSMENT

At its 45th session in May 2019, the CCFL asked FAO and WHO to provide scientific advice relating to the list of foods and ingredients in section 4.2.1.4 of GSLPF on (FAO and WHO, 2019):

- Whether the published **criteria** (FAO and WHO, 2000) for assessing additions and exclusions to the list are still current and appropriate
- Subject to the advice on the criteria above:
  - whether there are foods and ingredients that should be added to or deleted from the list;
  - clarification of the groupings of foods and ingredients in the list; and
  - whether certain foods and ingredients, such as highly refined foods and ingredients, that are derived from the list of foods known to cause hypersensitivity, can be exempted from mandatory declaration.

Food ingredients to be considered for addition include those identified by the electronic working group which prepared the Code of Practice on Food Allergen Management for Food Business Operators (FAO and WHO, 2018b), (i.e. sesame seeds, buckwheat, celery, mustard, molluscs and lupin).

TASK 2 REVIEW AND ESTABLISH THRESHOLD LEVELS IN FOODS OF THE PRIORITY ALLERGENS

At its 50th session in November 2018, the CCFH asked FAO and WHO to provide scientific advice relating to threshold levels in foods of the priority allergens as below (FAO and WHO, 2018b):

- What are the threshold levels for the priority allergens below which most allergic consumers would not suffer an adverse reaction?
- How can thresholds be used by food business operators (FBOs) to determine:
  - the extent to which a cleaning procedure removes an allergen to a level that prevents or minimizes the risk to most allergic consumers from allergen cross-contact; and
  - whether an ingredient that contains a low level of an allergen warrants control of its use to prevent or minimize allergen cross-contact?
- What are appropriate analytical methods for testing food and surfaces?

TASK 3 REVIEW AND EVALUATE THE EVIDENCE IN SUPPORT OF PRECAUTIONARY LABELLING

The 50th session of CCFH also asked for scientific advice on:

- What methods/tools are available for FBOs to determine:
  - whether allergen cross-contact is reasonably likely to occur in a food after a cleaning procedure;
  - whether allergen cross-contact is reasonably likely to occur from equipment used for foods with different allergen profiles; and
  - the level of allergen in a food resulting from cross-contact.

In relation to the ongoing work of CCFL, the task will also include:

- Guidance on precautionary labelling:
  - Use scientifically based threshold levels to evaluate risk for consumers with food allergies.
  - Determine the conditions for using precautionary allergen labelling.

1.3. EXPERT CONSULTATION

This report focuses on deliberations and conclusions of an ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens, held virtually from 30 November to 11 December 2020, 28 January and 8 February 2021. The objective of this first meeting was to validate and update the list of foods and ingredients in section 4.2.1.4 of the GSLPF based on risk assessment (Task 1).

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CHAPTER 2
CRITERIA FOR SELECTING PRIORITY ALLERGENS

The Expert Committee extensively discussed the criteria that should be taken into consideration for the selection of priority allergens. As a first step, the Committee discussed the different types of diseases related to food and gluten.

2.1. DISEASES TO BE CONSIDERED BY THIS AD HOC WG

The Expert Committee identified that food hypersensitivity disease consideration for the established criteria would primarily be given to IgE-mediated food allergies and coeliac disease since these diseases are well documented to cause serious adverse public health outcomes. While food allergen data in relation to other immune-mediated responses to food (e.g. eosinophilic gastroenteropathies, food protein-induced enterocolitis syndrome) exist and were also considered in the criteria assessment for prevalence (and severity), these data were not found to be sufficiently robust with regards to prevalence, potency or severity and thus were only secondary considerations. Non-immune-mediated diseases like lactose intolerance and fructose malabsorption were not considered by the Committee owing to lack of sufficient comparative food allergen data and lack of documented evidence that these diseases cause serious adverse public health outcomes (**Figure 1**).

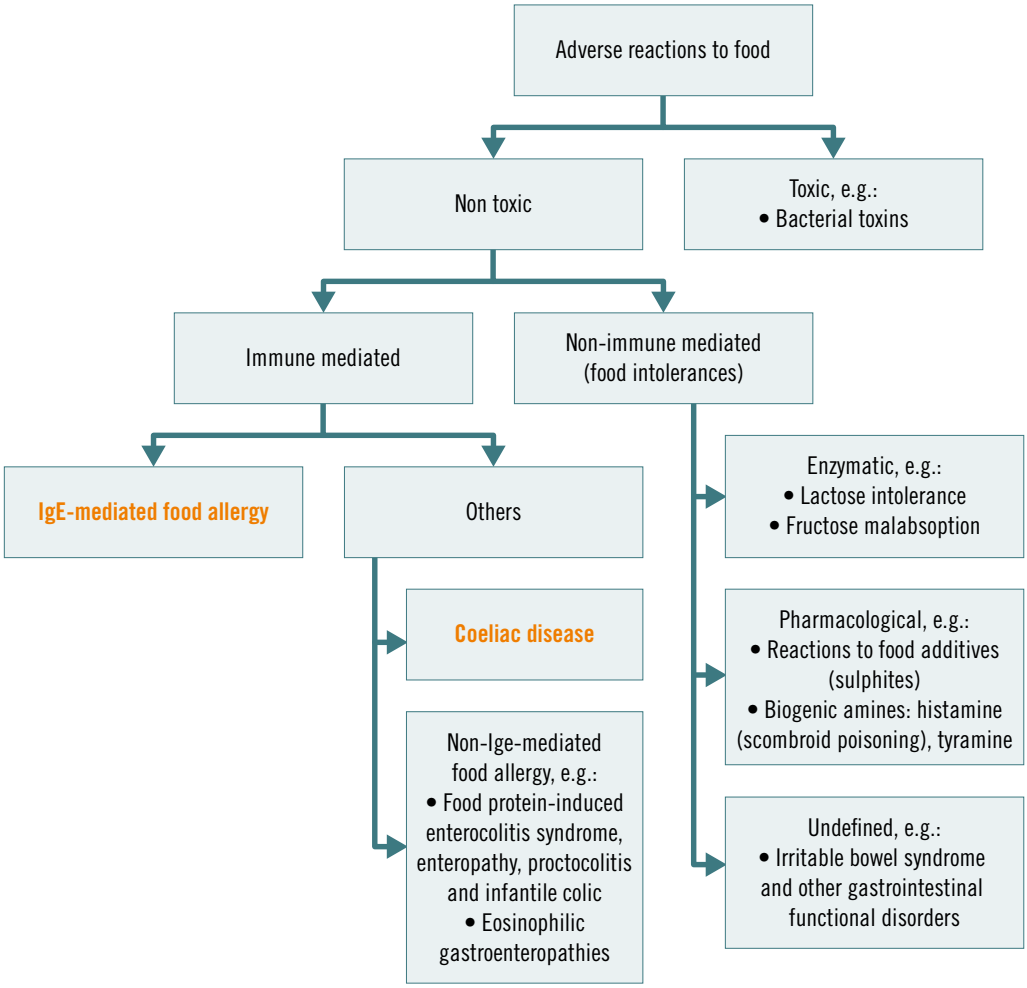
2.2 EXTENDED DEFINITION DISEASES

For this report, food allergy, coeliac disease and food intolerances are defined as follows, and **Annex 1** provides more details and other definitions:

2.2.1 FOOD ALLERGY

> Food allergy is defined as an adverse health effect arising from a specific immune-mediated response that occurs reproducibly on oral exposure to a given food, which may or may not be mediated by food-specific immunoglobulin class E (IgE) antibodies.

FIGURE 1. **DIFFERENT TYPES OF DISEASES RELATED TO FOOD ALLERGENS AND GLUTEN**



Source: Authors' own elaboration.

> IgE-mediated food allergic reactions usually occur < 2 hours after ingestion of a food and may manifest with a variety of signs and symptoms that can involve the digestive, respiratory, cardiovascular or cutaneous organ systems. The severity of reactions varies from mild (e.g. hives) to severe (e.g. life-threatening anaphylaxis). If not promptly treated, anaphylactic reactions can be fatal.

> Immune, non-IgE-mediated food allergies (such as cell-mediated immune responses to food allergens) more commonly affect only the gastrointestinal tract in a subacute or chronic way and are typically delayed in onset (> 2 hours). The primary disorders in this category include food protein-induced enterocolitis, food protein-induced proctitis/proctocolitis and eosinophilic enteropathies.

The mainstay of treatment is allergen avoidance together with rescue medication for those at risk of severe reactions. Although immunotherapies are becoming available, they are not curative and still require individuals to avoid consuming problem foods.

2.2.2 COELIAC DISEASE

> Coeliac disease is a chronic immune-mediated intestinal disease in genetically predisposed individuals induced by exposure to dietary gluten proteins that come from wheat, rye, barley and triticale (a cross between wheat and rye).

> For people with coeliac disease, consuming gluten causes inflammation and damage to the lining of the small intestine which may directly lead to diarrhea or constipation and other significant gastrointestinal symptoms but may also prevent absorption of key nutrients leading to severe anemia, osteoporosis or developmental delays in children. As the disease progresses with continuing exposure to gluten, long-term complications can occur. Many organ systems can be involved, including the gastrointestinal, skeletal, reproductive (infertility) and nervous systems (ataxia and neuropathy). Individuals with untreated coeliac disease also have an increased risk of certain cancers.

> For people with coeliac disease, the prolamins found in wheat (gliadins and glutenins), rye (secalins) and barley (hordeins) are of most concern. In other groups of individuals, gluten (gliadins and glutenins) and some other proteins (albumins and globulins) from wheat can also trigger serious IgE-mediated allergic reactions. However, data are often lacking as to whether homologous protein types from rye and barley also cause IgE-mediated reactions.

> The only current treatment for coeliac disease is maintaining a lifelong strict gluten-free diet. However, IgE-mediated allergy is distinctly different from coeliac disease.

2.2.3 FOOD INTOLERANCES

> Food intolerances are non-immune-mediated adverse reactions. They can be categorized into three types: enzymatic, pharmacological and undefined or idiopathic food intolerances. The most common foods implicated in intolerances include dairy products, products containing sulphite, salicylates, FODMAPs (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols), biogenic amines, lactose, and food additives.

2.3 CRITERIA FOR SELECTING PRIORITY ALLERGENS

The Expert Committee deliberated which criteria should be considered when selecting priority allergens. While potentially many aspects can be taken into account, the Committee agreed to consider the aspects summarized in **Table 1**.

TABLE 1 **THE SELECTED CRITERIA**

CRITERION	REASONING
Evidence that a food can cause an immune-mediated adverse reaction to food	If answer is no, "N", it's outside the scope. Suggested grading of evidence and coding of foods is shown below and only include foods which have evidence that meets grades 1–3.
Prevalence	Evidence should be graded according to quality and in particular, the nature and quality of the diagnosis used to define whether individuals have an immune-mediated adverse reaction to food. Geographic variations are wide as is the impact of age on prevalence to specific foods.
Potency	There is now good to very good evidence that the proportion of individuals allergic to a food who react on challenge is a function of the amount or dose of allergenic protein ingested.
Severity vs potential (long term) health impact	Severity is a complex and multidimensional construct and subject to significant variation in perception of severity, both by different stakeholders and even among different members of the same stakeholder group. Most constructs support that severity of food allergy is exemplified by the type and frequency of objective allergic reactions or other serious adverse health outcomes experienced by individuals allergic to a particular food and that anaphylaxis is a severe allergic reaction. However, biomarkers of allergic reaction severity and the relationship between allergen dose or potency and severity of reaction or anaphylaxis, at least for an IgE-mediated food allergy, remain poorly defined. The proposal is to use real-world data on frequency of anaphylaxis to allergens (reported reactions to registries, presentations to a healthcare facility and admissions to intensive care and/or fatal outcomes). Use of this outcome also facilitates an assessment of how these allergens may vary in different geographical regions.

The Expert Committee discussed the inclusion of several additional factors such as regional prevalence and potential exposure to and/or potential for hidden or undeclared allergens (e.g. the likelihood that an allergen can be present in food products as an ingredient or other quantity, and the allergen source is not labelled or easily identified by allergic individuals). Hidden allergens may occur because of certain loopholes in labelling regulations. However, the aforementioned reasons were not considered for the selection of priority allergens of global relevance.

2.3.1 EXTENDED REASONING FOR INCLUSION/EXCLUSION

The grading of evidence that a food can trigger an immune-mediated adverse reaction to food, adapted from Mills *et al.* (2013), are as follows:

> **Grade 1:** The food is well-characterized, and food fractions and food protein-derived toxic motifs inducing a clearly defined adverse reaction acting through a defined immunological mechanism are present.

- **Grade 2:** There is a clear, food-induced reaction, but food fractions or motifs evidenced by oral challenges are missing. The disease is less well described mechanistically, although it is evident that it has an immune mechanism.
- **Grade 3:** There is a clear, food-induced reaction, but implicated foods may not be so well described, and whilst the immune system is implicated, a clear causal biological mechanism causing the adverse reaction is lacking. Food is implicated through application of elimination diets.
- **Grade 4:** The food is implicated as a causative agent but is not well defined and may not be the sole cause of adverse reactions involving the immune system.
- **Grade 5:** There is poor evidence that the food acts as a specific trigger of an immune-mediated adverse reaction although diet has been implicated as a factor.

2.3.2 PREVALENCE

Definition: the proportion of a defined population known to have experienced an immune-mediated adverse reaction to food. It can be expressed as:

- **Point prevalence:** the proportion of the population expressing a reaction at a given point in time
- **Period prevalence:** the proportion of the population expressing a reaction during a given period
- **Lifetime prevalence:** the proportion of the population that will experience an immune-mediated adverse reaction to food at some point during their lifetime

The prevalence can vary by population group, age, place and time, and study designs need to take account of this to determine prevalence in an unselected study population, representative of the population under study with regards to gender, age and ethnicity, and so on. Consideration needs to be paid to the diagnostic method used and whether it is appropriate for determining the prevalence of a given immune-mediated adverse reaction to food.

To date, studies conducted to estimate prevalence of IgE-mediated food allergies in various global populations have relied on a variety of different diagnostic methods or assessment factors. These may include studies which recruit subjects with food allergies verified by food challenges or whose adverse food reaction history is verified by sensitization to IgE antibodies or positive skin prick testing (SPT). Other studies may determine food allergy only by self-reported data, evidence of sensitization to the food alone, or by retrospective review of medical records in individuals with an International Classification of Disease (ICD) diagnosis of a possible food allergy. Depending on which methods or factors are used, the estimated population prevalence for individual food allergens can vary greatly between studies (Boyce *et al.*, 2011; Muraro *et al.*, 2018) and makes determining or comparing true prevalence for each food difficult. Because of these differences, the quality of individual prevalence studies has been reviewed and graded against the accuracy of an IgE-mediated food allergy diagnosis and prevalence estimation (Björkstén *et al.,* 2008).

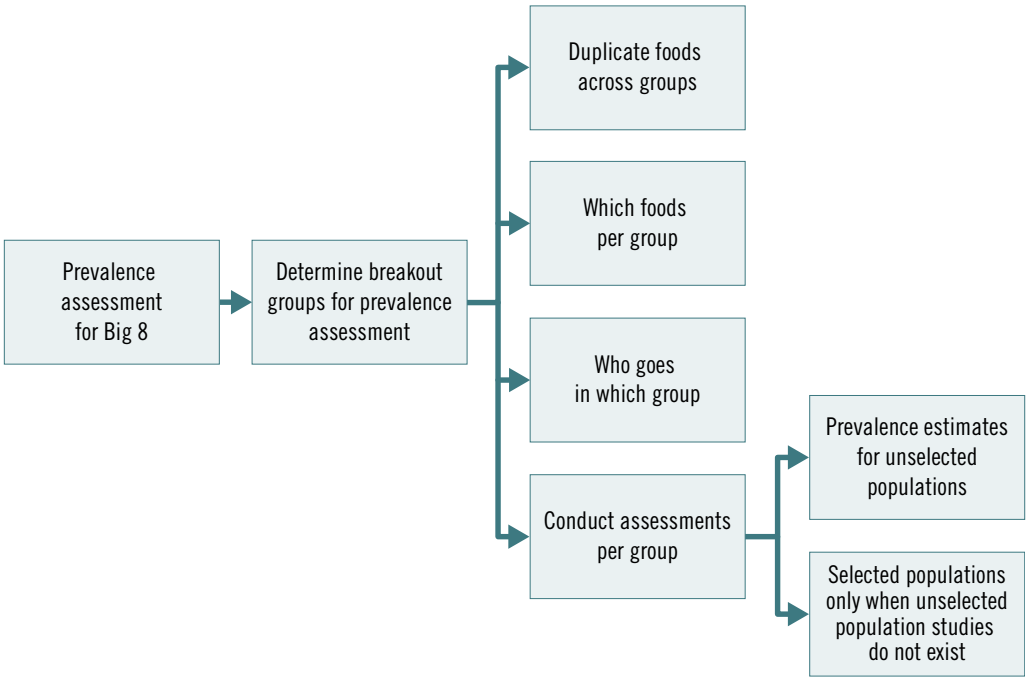
The Expert Committee reviewed these grading approaches and agreed on the following approach (**Figure 2**) to grading the quality of prevalence data for this global prevalence assessment:

> **Grade 1:** There is a prevalence of confirmed adverse reaction to foods using appropriate "gold standard tools" such as a combination of clinical history, sensitization to food (determined by skin prick test > 3 mm wheal diameter and/or food allergen specific IgE > 0.35 kU/L) and oral food challenge, or anti-tissue transglutaminase 2 (TG2) IgA, with anti-endomysial IgA being employed as a confirmatory test and intestinal biopsy as a confirmation in equivocal cases to define coeliac disease.

> **Grade 2:** There is a probable adverse reaction to foods with symptoms consistent with a particular immune-mediated adverse reaction to food and evidence of a disease biomarker, e.g. sensitization to a relevant food determined by SPT (> 3mm wheal diameter) or food allergen specific IgE (> 0.35 kU/L) for an IgE-mediated food allergy.

> **Grade 3:** There is a possible adverse reaction to food based on self-report data alone with or without evidence of symptoms consistent with IgE-mediated reaction, and there is a reported doctor diagnosis of food allergy, etc., or the food allergy is based solely on evidence of IgE sensitization to the food alone. Food allergic individuals are identified by registries or retrospective review of medical records with or without ICD diagnosis of possible food allergy.

FIGURE 2. **ASSESSMENT PLAN FOR DETERMINING PREVALENCE**



Source: Authors' own elaboration.

In general, evidence of grade 1 or grade 2 is considered to provide the most robust and reliable prevalence estimations for IgE-mediated food allergy diagnosis in the population. Evidence of grade 3 is considered to overestimate true IgE-mediated food allergy prevalence estimates as data from these studies may not reflect true diagnosis and thus include data from individuals with other food hypersensitivities or symptoms mistaken for IgE-mediated allergies.

2.3.3 POTENCY

Allergenic potency: evidence of a credible cause-effect relationship establishing that the food causes food allergies and supported by DBPCFC studies designed to assess the elicitation potency of an ingredient (whatever the severity of the objective symptoms reported). The (lowest) amount of total protein from the allergenic food triggering objective symptoms should be documented.

"Potency can be described either as the 'frequency dose-response' defined as the population distribution of doses eliciting or provoking a reaction, or as the 'severity dose-response' denoting the gradient of severity of reactions caused by the food." (Operational definition used in Björkstén *et al.*, 2008 – currently only the first part [frequency-dose response] is used in practice, and severity is dealt with separately). The critical attribute is variation of frequency of response with amount/dose of total food protein from the allergenic source.

Grading of quality of evidence for potency was proposed in Björkstén *et al.*, 2008 and refined in van Bilsen *et al.*, 2011.

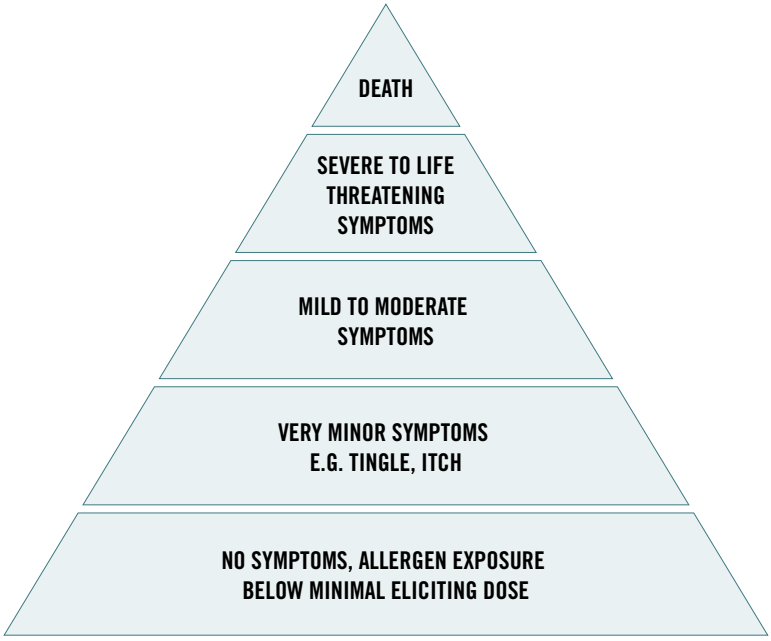
ED50 (median population MED) was proposed as the quantitative attribute for comparing potency as an indicator of the public health importance of an allergenic food in Houben *et al.* 2016, the other attribute being prevalence.

2.3.4 SEVERITY

The management of patients at risk of food-induced allergic reactions involves multiple individuals and organizations: patients and their caregivers, healthcare professionals, researchers, regulatory authorities and food businesses. The accurate assessment and communication of reaction severity between these different stakeholders is key to management. However, severity can mean different things to different stakeholders (Turner *et al.*, 2016). Numerous severity grading systems for allergic reactions have been developed to help address some of these issues; however, there is a lack of consensus on how to define severity, particularly with respect to food allergy (Turner *et al.*, 2016; Muraro *et al.*, 2018; Arasi *et al.*, 2020). Importantly, while anaphylaxis is recognized to be a severe manifestation of an IgE-mediated food allergy, this condition can have various clinical presentations and health outcomes – many of which may not necessarily be linked to a severe or serious impact to the overall health of individuals.

Importantly, there are different severity considerations for IgE-mediated vs non-IgE-mediated food allergies. With respect to the former, the spectrum of severity is better defined, ranging from mild subjective allergic symptoms to fatal anaphylaxis (**Figure 3**). However, symptoms of non-IgE-mediated allergies are (with a few notable exceptions) non-acute and rarely life-threatening. Non-IgE-mediated food syndromes include food protein-induced allergic proctocolitis, food protein-induced enterocolitis (FPIES) and food protein-induced enteropathy syndrome as well as eosinophilic gastrointestinal disorders such as eosinophilic esophagitis (EoE), allergic eosinophilic gastroenteritis and eosinophilic colitis (Calvani *et al.*, 2021). Most are associated with abdominal and/or dermatological manifestations, and in chronic severe cases result in growth failure. However, except for severe EoE causing oesophageal strictures and severe FPIES, these syndromes are not in themselves life threatening. Coeliac disease is an immune-mediated food hypersensitivity in which gluten exposure in affected individuals causes immune-mediated gastrointestinal inflammation and associated symptoms and has been linked to an increased risk of lymphoma. However, acute, life-threatening manifestations are very rare.

FIGURE 3. **HIERARCHY OF RISKS FACED BY PEOPLE SUSCEPTIBLE TO IGE-MEDIATED FOOD ALLERGY**



Source: Reproduced with permission from Dubois *et al.*, 2018.

Therefore, while each condition has different concepts of severity and health impacts at the individual and societal level, for the purpose of prioritizing food allergens on the basis of public health importance, a metric for severity at the population level should be utilized.

2.4 CRITERIA FOR DERIVATIVES RECOMMENDED TO BE EXEMPTED FROM LABELLING

Many ingredients are derived from the foods included on the priority list (Bush, Baumbert and Taylor, 2020). Some ingredients contain comparatively high levels of protein from the source food (e.g. casein from milk, gluten from wheat and marzipan from almonds), while others contain almost non-detectable levels of protein from the source food (highly refined peanut oil, butter ester from milk and ethanol from wheat starch). The names of some of these ingredients (e.g. casein, whey and semolina) do not allow easy identification of the source food. Ideally, source labelling of derivatives of the foods on the priority list should be based upon the hazard posed to consumers who are allergic to that source food. Labelling exemptions should be based upon the degree of risk using available scientific and clinical data and should also be considered on a case-by-case basis.

Decisions regarding exemptions from source labelling can be based upon several criteria as outlined in **Table 2**.

TABLE 2 **CRITERIA FOR DERIVATIVES RECOMMENDED TO BE EXEMPTED FROM LABELLING**

CRITERION	REASONING
Level of protein unlikely to cause a reaction	IgE-mediated reactions are directed to the protein component of the food. Reduction of the protein content to an extent that the amount, if ingested, is below that known to trigger reactions in a (very) low proportion of at-risk individuals provides assurance of low probability of a reaction and thereby supports exemption. Expected frequency of reactions can be modelled to support the assessment. Requires the establishment of consensus threshold doses (Task 2). Requires demonstration that the selected analytical method is suitable to determine the protein content of the derivative.
Type of protein is unlikely to cause a reaction	While the allergenicity of a food is correlated with the total amount of protein from that source, some specific proteins are allergens while others are not. Requires demonstration that the ingredient will not elicit reactions upon challenge of allergic individuals.
Type vs degree of processing (e.g. hydrolysis) and distilled products	Exemptions based on process must be considered on a case-by-case basis and are likely limited. Requires demonstration that the selected analytical method is suitable to determine the protein content of the derivative. May require demonstration that the ingredient will not elicit reactions upon challenge of allergic individuals. Hydrolysis can reduce the probability of reaction, provided the process and its outcome are understood. For instance, it is likely to support lack of allergenicity if the fragments are too small to cross-link IgE and do not aggregate. This is evidenced by the efficacy of amino acid formula in the treatment of a cow's milk allergy. It can be assisted by other treatments such as high pressure, microwave or heat to increase its efficiency. Extensive hydrolysis is likely necessary. Distillation is a process used to separate volatile from non-volatile components of a mixture. Proteins are non-volatile compounds, so the distillate prepared from an allergenic food will contain extremely low levels of protein. Edible oil refining allows separation of the oil fraction from the meal fraction that is enriched in protein. Requires demonstration that the selected analytical method is suitable to determine the protein content of the derivative. Physical treatments can have opposite effects, depending on the intensity. For instance, heat treatments between 50 °C and 90 °C increase the allergenicity for some allergens, while temperatures above 90 °C could decrease the allergenicity for some allergens. It is unlikely that as sole treatments, they can suppress the allergenicity completely. This requires demonstration that the selected analytical method is suitable to determine the protein content of the derivative.

TABLE 2 **CRITERIA FOR DERIVATIVES RECOMMENDED TO BE EXEMPTED FROM LABELLING** (continued)

CRITERION	REASONING
Absence of clinical/ biological reactivity in affected individuals and biological reactivity	Absence of specific IgE-antibody binding, skin prick test reactivity and/or challenge reactions with the derivative provides good evidence to support exemption, particularly in situations where physico-chemical considerations (as above) are not considered conclusive.
Characterization/ specification of the derivative	The derivative for which an exemption is sought should be well-characterized and specified, e.g. in terms of limits to protein content and/or process (particularly important if the exemption is sought for a generic derivative rather than a proprietary one). Requires demonstration that the selected analytical method is suitable to determine the protein content of the derivative. For a generic derivative, assure that all commercial processes yield ingredients with similar compositions.

2.4.1 LEVEL OF PROTEIN

The amount of protein from the source food should be a key criterion for consideration for source labelling exemptions. In some circumstances this criterion has been oversimplified by equating it to a requirement of total absence of protein in products that are considered for such a labelling exemption. However, since the total absence of protein from any product can never be proven (all analytical methods have a detection limits), such an interpretation has been shown not to be especially useful. It is well established that some derivatives contain very little, if any, protein from the source, although difficulties with analytical methodology can limit the ability to quantify the precise amount of remaining protein. With the establishment of threshold doses in Task 2, the possibility will exist to establish a quantitative criterion that establishes a clear, hazard-associated basis for exemption decisions based upon the protein content of a specific derivative. The level of protein unlikely to cause a reaction can be compared with established threshold doses (Task 2) defined by the dose distribution of individual minimum eliciting doses (MEDs) for the allergenic food where such data are available. Some considerations in using the data would be whether the protein concentration in the derivative had just been reduced, or its profile had been altered during the process (this would affect analytical methods in relation to the calibrants used, among other factors).

A select few derivatives may be considered for source labelling exemptions, even though these ingredients contain high levels of protein from the source food. In these specific cases, the derivative is composed of proteins other than the known prevailing allergens from the source food. The best example is fish gelatin, which is composed primarily of collagen, a fish protein with limited allergenic potential. The predominant allergen in fish is parvalbumin, a calcium-binding protein from fish muscle. Fish gelatin is manufactured primarily from fish skins that contain limited amounts of adherent fish muscle tissue. Parvalbumin levels can be reduced to levels below detection limits by extensive water washing of the insoluble gelatin material (Koppelman *et al.*, 2012). Considerable caution is needed in applying this criterion because of the uncertainty about the level of water washing that is applied by fish gelatin manufacturers overall. Glucose syrups from wheat constitute another example. Although they contain measurable residual protein, this is largely

granule-based starch synthase (GBSS) rather than gluten (EFSA, 2007). Additionally, specific exemptions could be applied for certain uses of such derivatives. Fish gelatin again serves as an example because one use is the encapsulation of vitamins, a use that leads to very low consumer-exposure doses. A clinical challenge trial was conducted on codfish gelatin to document that the levels of this derivative typically used for vitamin encapsulation did not provoke allergic reactions in cod-allergic individuals (Hansen *et al.*, 2004).

2.4.2 DEGREE OF PROCESSING

Demonstration of the absence of biological/clinical reactivity can support a source labelling exemption and may indeed be essential if other data are inconclusive. Critical methodological considerations will include choice of population in which to test, possibly featuring at least a high proportion of individuals with a high degree of reactivity, as well as enough to enable derivation of a statistically robust conclusion. Participants should also be well characterized in terms of their allergic reactivity.

The evaluation of the effect of processing operations on the allergenicity of a food or an ingredient derived from that food is complex. The demonstration of a lack of clinical reactivity is likely necessary to confirm that the process has eliminated or sufficiently reduced the allergenic hazard. Processing can affect the solubility of allergenic proteins, removing them from solution and complicating the detection of residual allergens. Insoluble allergen residues, while often undetectable by many analytical methods, may retain allergenicity upon oral challenge because digestion succeeds in resolubilizing the aggregated allergenic proteins. Even biological reactivity measures such as IgE binding can be misleading due to the insolubility of the allergenic proteins. Several processing methods do have documented capability of reducing or eliminating the allergenic hazard: oil separation and refining, hydrolysis and/or fermentation, and distillation.

Many edible oils for food use are highly refined (Crevel, Kerkhoff and Koning, 2000). In this process, solvents (e.g. hexane) are used to separate the oil fraction from the meal fraction containing the protein (allergen) components from the source food. The oil is then further refined by neutralization, bleaching and deodorizing. Any remaining protein residues are largely removed by these latter refining steps. Highly refined oils (e.g. peanut and soybean) contain very low levels of protein barely above detectable limits by the most sensitive analytical methods (typically < 0.1 ppm). Fish oil also contains low levels of residual protein. Clinical challenge trials have demonstrated the safety of highly refined peanut and soybean oils for peanut-allergic and soybean-allergic individuals, respectively (Hourihane *et al.*, 1997; Bush *et al.*, 1985). Fish oil has also been documented to be safe for fish-allergic individuals (Mark *et al.*, 2008). Some edible oils are cold-pressed (also called expeller-pressed) such as sesame oil, and these oils are not considered to be safe for allergic individuals. The extraction method, which may differ from one production of sesame oil to another, could explain the reported variation in allergenicity (Agne *et al.*, 2003). However, the analysis of protein or allergen

levels in oils is difficult (Crevel, Kerkhoff and Koning, 2000; Rigby *et al.*, 2011) since many existing analytical methods rely upon aqueous protein extraction, which is likely inefficient with oil matrices. Degree of hydrolysis will be a critical factor in determining whether a derivative produced by hydrolysis or fermentation meets the criteria for exemption. A mild process may leave protein fragments of a size able to trigger reactions, but if the process results in fragments too small to cross-link specific IgE, this would provide support for exemption of the derivative. The degree of hydrolysis may be characterized by biochemical techniques, such as the spectrum of peptide molecular weights or the ratio of a-amino nitrogen to total nitrogen (Vandenplas and Salvatore, 2016). Immunological methods with sufficient sensitivity to allow detection at low levels of biological importance could also be used to demonstrate either absence of detectable proteins or levels lower than those eliciting doses. However, the detection of allergen residues in hydrolysates is quite challenging because many analytical methods rely on detection of the intact protein and will yield false negative results with hydrolysates. An indicative size based on studies with hydrolysed infant formulae suggests 3.5 kDa might be a valid limit. There is also data from development of vaccines indicating that the immune system is unable to mount a strong humoral response towards peptides of less than ~13 amino acids in length (Purcell *et al.*, 2003). Furthermore, for a peptide to trigger an effector cell to release its contents, an event at the heart of an allergic reaction needs to be large enough to comprise at least two IgE epitopes (Holowka *et al.*, 2007).

For the production of infant formulas based on cow's milk protein hydrolysates, it is considered that hypoallergenic clinical performance can be achieved at residual allergen concentrations below 15 µg/mL, although the most effective products contain less than 1 µg of allergen/mL (Koppelman and Hefle, 2006). It is also suggested that analytical methods to analyse milk proteins have quantitative sensitivity limits in the range of 100 ng/mL. A recent survey showed the majority (but not all) of a panel of extensively hydrolysed formulas contained residual β-lactoglobulin and casein consistent within these limits (Nutten *et al.*, 2020). However, concerns about the capacity of larger peptides or peptide aggregates to cross-link IgE and trigger histamine release has led to a new generation of effector cell based tests (Knipping *et al.*, 2016).

Fermentation processes are widely used in the food industry for the production of many foods (e.g. cheese, bread, beer). If the fermentation process involves extensive proteolysis, it may lead to elimination or reduction of the allergenicity of the source food. However, many food fermentations primarily involve the degradation of carbohydrates such as starch and sugars. These fermentations have little effect on the allergenicity of the derivative, such as cheese resulting from the fermentation of lactose in milk remains allergenic). The best example of a proteolytic fermentation that yields a derivative with a very reduced level of allergenicity is soy sauce, made by a mold fermentation of soy and wheat (Bush, Baumbert and Taylor, 2020; Kobayashi, 2005).

Distillation is perhaps the best example of a process that separates allergenic proteins from the derivative of interest. One example is the fermentation of wheat starch

to yield ethanol that can be distilled to manufacture high purity ethanol with no detectable wheat protein residues. Distilled spirits (e.g. vodka and rye whiskey) are other distilled products with no detectable gluten residues. Several flavouring agents are derived from milk in part through distillation; examples are butter ester and starter distillate.

2.4.3 ABSENCE OF CLINICAL/BIOLOGICAL REACTIVITY IN AFFECTED INDIVIDUALS AND ANIMAL MODELS

It is possible to demonstrate changes in allergenic activity in terms of eliciting an allergic reaction in sensitized individuals. Thus, clinical oral challenge trials involving appropriate amounts of a derived food ingredient in individuals with well-defined allergies to the source food of the derived food ingredient remain the gold standard approach to document that the allergenic activity of the derived ingredients is low enough to pose little to no risk to allergic consumers and can therefore be exempted from allergen labelling regulations. Oral challenge studies have the advantage of being holistic approaches since digestion, absorption, IgE-binding on effector cells, mediator release and mediator responses are considered. Other measures of biological reactivity, short of an oral challenge trial, which may also be useful include skin prick testing, mast cell or basophil activation tests and IgE-binding studies. These approaches are not as definitive as oral challenge trials. Well-validated animal models do not exist that allow the prediction of the allergenicity of ingredients in terms of *de novo* sensitization.

2.4.4 CHARACTERIZATION/SPECIFICATION OF A DERIVATIVE INGREDIENT

For generic exemptions, such as those which might pertain to a whole class of products, characterization of the material used to demonstrate the absence of potential or actual allergenic reactivity is essential. This characterization should cover the relevant characteristic(s), such as the level of residual protein and be used to develop a relevant specification. This could include a detailed description of the process (e.g. refining of edible oils), a value for the relevant criterion (e.g. level of protein), together with a demonstration that the selected analytical methods are validated to demonstrate compliance. The EFSA opinion on highly refined soybean oil shows how this approach can be applied in practice (EFSA, 2007).

To conclude, establishing that a product derived from an allergenic food does not pose a risk to consumers with allergies to that food and therefore merits exemption from labelling requirements appears conceptually simple, insofar as it requires that absence of protein be demonstrated and/or inability of residual protein to trigger reactions in susceptible individuals. However, the absence of protein is impossible to prove standard methodologies. Analytical methods can be exceptionally sensitive and may detect gluten residues that are not clinically relevant, while other methods may not be validated adequate to detect presence or absence of certain protein residues that are highly processed. Furthermore, the demonstration of clinical

and/or biological reactivity can be very complex indeed. Thus, the practical aspects of demonstrating these outcomes have required a diversity of approaches, the interpretation of the results and the criteria applied to the interpretation can be a matter of debates and uncertainty. Even in cases where extensive research has been performed (e.g. the use of milk protein hydrolysates in hypoallergenic infant formula), there remains debate about the extent to which the desired outcomes have been achieved. A generic approach applicable in all, or even most cases, still remains beyond reach, and mandates case-by-case evaluation. However, with the establishment of thresholds in Task 2, this situation should be reconsidered as part of Task 3.

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CHAPTER 3
PREVALENCE OF IMMUNE-MEDIATED ADVERSE REACTIONS TO FOODS

3.1 INTRODUCTION

Non-toxic adverse reactions to foods can be classified based on their etiology as either being immune- or non-immune-mediated (or so-called food intolerances) (see **Annex 1** for further information).

Since the mainstay for treating all types of immune-mediated adverse reactions is avoidance of the offending food, supporting consumers in making safe food choices through labelling of the major food triggers is important. Consequently, the prevalence of a disease is an important factor to consider in relation to determining foods of public health importance since such data define the size, age, gender and ethnicity of the population at risk (Björkstén *et al.*, 2008). It can also allow identification of environmental factors that may influence patterns and prevalence of a disease in different geographic or climatic regions of the world. There are inherent biases in the way in which patients get referred into healthcare systems across the world, and consequently, it is crucial that the prevalence of a disease is determined in an unselected study population using a sample frame designed to capture a representative proportion of the population under study with regards gender, age, ethnicity and socioeconomic status (Celentano, Szklo and Gordis, 2019).

Of the immune-mediated adverse reactions to foods considered to be within the scope of the consultation, only coeliac disease and IgE-mediated adverse reactions to foods will be considered with regards to their prevalence. Those excluded are summarized in **Table 3** and were excluded because some conditions are very rare whilst for others, data were lacking on prevalence in unselected populations with rigorous diagnostic outcomes. Further background information on these conditions and their classification can be found in **Annex 1**.

TABLE 3 **SUMMARY OF PREVALENCE OF NON-IGE-MEDIATED FOOD ALLERGY NOT INCLUDED IN THE ASSESSMENT**

CONDITION	PREVALENCE/INCIDENCE	FOOD TRIGGERS	REFERENCES
Food protein-induced enterocolitis syndrome (FPIES)	Incidence ranges from 0.34% at 1 year in Israel to 0.51% (95% CI, 0.42–0.62) in the United States of America but is very low in an Australian study using a rigorous case (15.4/100 000/y. incidence in infants under the age of two years).	Commonly milk and soybean and cereals	Katz *et al.*, 2011; Nowak-Wegrzyn *et al.*, 2019; Mehr *et al.*, 2017
Food protein-induced enteropathy	A rare condition the prevalence of which has not been determined.	Cow's milk, soybean, egg, fish, cereals (including wheat and rice)	Caubet *et al.*, 2017; Savilahti, 2000
Food protein-induced allergic proctocolitis	Prevalence isestimated to be around 0.16% in Israel and a cumulative incidence over 3 years of 17% in the United States of America.	Cow's milk, soy	Elizur *et al.*, 2012; Martin *et al.*, 2020
Eosinophilic oesophagitis	Incidence is estimated to be 4.37 (95% CI: 3.94–4.84) vs 1.97 (95% CI: 1.68–2.29) per 100 000 males and females, using a disease registry in Netherlands. Incidence is higher in the United States of America at 56.7/100 000.	Cow's milk, wheat, egg, soy and meats	de Rooij *et al.*, 2021; Dellon *et al.*, 2014
Non-eosinophilic oesophagitis gastrointestinal diseases (eosinophilic gastroenteritis; eosinophilic colitis)	Very rare conditions are estimated to affect 2% of patients with gastrointestinal disease.	Food triggers are not well defined since conditions do not respond well to elimination diets, although biomarkers (such as eosinophil counts) respond to such treatments in children.	Licari *et al.*, 2020; Cianferoni, 2020

The second aspect that will affect the quality of the prevalence data is the method used to diagnose a particular condition. The diagnostic methods for the different types of immune-mediated adverse reactions that are within the scope of the consultation are summarized below.

3.1.1 COELIAC DISEASE

Coeliac disease and the associated conditions, dermatitis herpetiformis and gluten ataxia are immune-mediated adverse reactions where the symptoms resolve or stabilize following adherence to a gluten free diet (Husby *et al.*, 2012; Murch *et al.*, 2013). Symptoms of the condition are typically manifested as a malabsorption syndrome with weight loss and fatigue together with gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea and flatulence. Individuals with these conditions who are on a gluten-free diet suffer a relapse within several hours of being challenged with gluten (or purified gluten fractions), the appearance of symptoms being preceded by immune, cell-mediated inflammatory changes and associated with a flattening of the intestinal mucosa (Ensari *et al.*, 1998; Kristjansson *et al.*, 2005). Also, chronic exposure to gluten-containing grains may lead to persistent intestinal

inflammation resulting in severe nutrient deficiencies such as iron-deficiency anemia, osteomalacia, osteoporosis, and failure to thrive as well as in potentially fatal gastrointestinal malignancies. More detail on coeliac disease and associated conditions can be found in **Annex 1**.

Diagnosis of coeliac disease involves:

> **HLA typing:** The HLA types HLA-DQ2 and/or HLA-DQ8 are predisposing risk factors for coeliac disease; although HLA typing may be undertaken to support diagnosis, it is not sufficient alone. These genetic markers (HLA-DQ2 and/or HLA-DQ8) allow exclusion of a diagnosis of coeliac disease when they are negative.

> **Serological analysis:** This relates to the determination of anti-tissue transglutaminase 2 (TG2) and anti-endomysial IgA (Volta and Villanacci, 2011). False positives can be observed for the TG tests due to raised levels of IgA in patients with inflammatory bowel disease, food allergy, irritable bowel syndrome, giardiasis, other intestinal infections and autoimmune disorders.

> **Intestinal biopsies:** Intestinal biopsies to determine mucosal damage remain the preferred approach for confirmation of coeliac disease using, for example, the Marsh grading system (Husby *et al.*, 2012; Murch *et al.*, 2013; Oberhuber *et al.*, 1999; Lewis and Scott, 2010). This provides an unequivocal diagnosis but requires patients to continue with a gluten-containing diet prior to biopsy; many are unable to comply with this. There are recommendations that individuals with a 10-fold elevated IgA level to TG2 accompanied by anti-endomysial IgA and who are HLA-DQ2 and/or HLA-DQ8 type do not require a biopsy (Murch *et al.*, 2013; Caio *et al.*, 2019).

3.1.2 IGE-MEDIATED ADVERSE REACTIONS TO FOOD

Diagnosis of IgE-mediated food allergies encompasses the taking of a detailed clinical history which includes aspects of eliciting allergens and timing of appearance of symptoms, which should appear within two hours of consumption of an offending food. Other aspects to be considered include the signs and symptoms, whether they are characteristic of an IgE-mediated food allergy, and their severity. Other important considerations include whether the reaction is reproducible, and aspects such as family history of allergic disease and coexisting medical problems such as other allergies and asthma. The second aspect of diagnosis is the determination of food specific IgE either through skin prick testing or the determination of allergen specific serum IgE. However, since IgE sensitization does not always predict clinically relevant food allergy, such allergy testing has to be determined by the clinical history and helps to confirm whether a patient has IgE to a particular problem food. The gold standard of diagnosis is oral food challenge, and in particular, double-blind placebo-controlled food challenge (DBPCFC) and provides objective diagnosis of IgE-mediated food allergy. Challenges are used clinically to demonstrate whether a patient is allergic or sensitized but tolerant and helps to inform dietary avoidance strategies (Bird *et al.*, 2020; Sampson *et al.*, 2012; Muraro *et al.*, 2014).

3.1.3 Criteria for quality evaluation of prevalence data

Taking into consideration diagnostic best-practice, the following approach to assessing the data quality has been taken. Starting with the highest quality of data, prevalence of challenge confirmed food allergy (grade 1) is generally greater than probable (grade 2) and greater than self-reported (grade 3) for both coeliac disease and IgE-mediated food allergy.

Grade 1: Prevalence of confirmed coeliac disease and IgE-mediated allergies is determined using appropriate "gold standard tools". These are:

- **IgE-mediated food allergy:** a clinical history of reaction to a food, together with evidence of sensitization to that food (determined by either skin prick test of > 3 mm wheal diameter and/or food allergen specific IgE of > 0.35 kU/L to that food) and a positive oral food challenge using that food with symptoms consistent with an IgE-mediated food allergy which appear in < 2 hours; and
- **Coeliac disease:** a combination of clinical history, anti-tissue transglutaminase 2 (TG2) IgA, with anti-endomysial IgA being employed as a confirmatory test and intestinal biopsy as a confirmation in equivocal cases to define.

Grade 2: Probable adverse reaction to foods with symptoms are consistent with a particular immune-mediated adverse reaction to food and evidence of a disease biomarker, such as sensitization to a relevant food determined by SPT (> 3 mm wheal diameter) or food allergen specific IgE (> 0.35 kU/L) for an IgE-mediated food allergy.

Grade 3: Possible adverse reaction to food is based on self-report data alone with or without evidence of symptoms consistent with IgE-mediated reaction and reported doctor diagnosis of food allergy, and so on. Food allergy is based solely on evidence of IgE sensitization to the food alone. Food allergic individuals identified by registries or retrospective review of medical records with or without ICD diagnosis of possible food allergy.

The approach adopted by the group was to consider ONLY grade 1 or 2 evidence because grade 3 evidence will give erroneously high prevalence estimates. Studies basing food allergy prevalence on IgE sensitization to food without any relationship to clinical history data were excluded since clinical diagnostic guidelines indicate that this is not good practice (Muraro *et al.*, 2014). This approach has also addressed the issue that routine clinical diagnosis of tree nut allergy can involve use of mixed tree nut reagents for skin testing, for example. The Expert Committee debated the relevance of grade 3 self-reported food allergy data and agreed that data from validated questionnaires also assessing symptoms and doctor diagnosis were potentially more robust for IgE-mediated food allergy diagnosis than questionnaires querying self-reported food allergy alone. The members also acknowledged that exclusion of these data could impact prevalence assessment of food allergies in certain geographic areas. However, a review of the literature identified sufficient grade 1 and 2 prevalence data to make global prevalence estimations for most food allergens. Thus, members ultimately decided that no grade 3 self-reported data met the scientific rigor for this prevalence assessment.

3.1.4 CLASSIFICATION OF PREVALENCE

The proportion of a defined population known to have experienced an immune-mediated adverse reaction to food can be expressed as:

> **Point prevalence:** the proportion of the population expressing a reaction at a given point in time

> **Period prevalence:** the proportion of the population expressing a reaction during a given period

> **Lifetime prevalence:** the proportion of the population that will experience an immune-mediated adverse reaction to food at some point during their lifetime

In general, most data assessed have only defined the point prevalence, although in some instances, data quality has allowed meta-analyses which have defined lifetime prevalence.

Assessment of the data indicates diverse prevalence rates around the world as a function of age group. Consequently, data have been assessed and classified to take this into account.

Age groups considered were:

> Infants and young children < 4 years

> Children aged 4–18 years old

> Adults

The classification of prevalence data into five categories is shown in **Table 4**.

TABLE 4 **CLASSIFICATION OF PREVALENCE OF IMMUNE-MEDIATED ADVERSE REACTIONS TO FOOD**

GROUP	GEOGRAPHIC CLASSIFICATION	DEFINITION AS % PREVALENCE
0	Insufficient data	Not applicable
1	Very low	< 0.5% in one region only OR < 0.1% in all regions
2	Low	< 0.5% in all regions
3	Mixed	> 1% in one region AND 0.5–1.0% in at least one other region
4	High	> 1.0% in more than one region

Prevalence data were classified using this approach for each age group, and then a consensus was arrived at over the overall prevalence score. Factors considered in this evaluation included whether a vulnerable group, such as infants or children, were showing a higher prevalence.

3.2 SUMMARY OF OVERALL PREVALENCE

GENERAL COMMENTS (Table 5)

- During the process of review, it became evident that prevalence studies often do not report negative results for very low prevalence foods; such data are informative in identifying allergenic foods of public health importance. It would be helpful if such information was made available in future prevalence studies for immune-mediated adverse reactions to food.
- The review process also identified that many parts of the world lack high quality grade 1 and grade 2 studies.
- There were six foods for which insufficient data were available to assign to a group. These were:
  - **Lupin:** This is not a widely consumed food, and it was added to mandatory allergen labelling lists in some regions and countries (European Union, Australia/New Zealand, Turkey, Morocco, Ukraine) because of potential cross-reactivity with peanut.
  - **Molluscan shellfish:** There is a lack of prevalence data where probable food allergy is reported, or allergy was confirmed by oral food challenge. It is not clear whether the lack of reported adverse reactions is because the food has not been included in the panels of food studies in epidemiology studies or because the prevalence is very low and has not been reported.
  - **Barley, rye and oats:** Studies on coeliac disease do not investigate reactions to these other cereals due to the known presence of coeliac toxic motifs in the seed storage proteins. There are few reports of IgE-mediated adverse reactions to them. Further information on this is included in **Annex 2**.
  - **Coconut:** There is a lack of prevalence data where either probable food allergy is reported, or allergy was confirmed by oral food challenge. Like for lupin, it is not clear whether the lack of reported adverse reactions is because the food has not been included in the panels of foods investigated specifically in epidemiology studies or because the prevalence is very low and has not been reported.
- Evidence was found that two foods, **egg and milk**, showed high rates of disease in young children in several geographic regions, although rates in adults are low or very low. A third food, **peanut**, also showed high rates in several geographic regions and the rates are higher in older children.
- Several foods showed mixed rates across the world, but prevalence was high in certain regions and included:
  - **Wheat:** only for triggering coeliac disease
  - **Tree nuts:**
    - **Cashew and pistachio**
    - **Hazelnut**

- Several foods (listed below) were classified as being of very low prevalence (listed below). For almond, Brazil nut, pecan and macadamia, there are few studies meeting grade 1 and 2 quality criteria which are limited to Europe and Australia.
  - Celery (regional – Eastern Europe)
  - Buckwheat (regional – Japan and the Republic of Korea)
  - Mustard
  - Almond
  - Brazil nut (regional – the United Kingdom of Great Britain and Northern Ireland and Australia)
  - Macadamia (regional – Australia)
  - Pecan
  - Pine nut (regional – Australia)
- The remaining foods are of a low prevalence.

Considering the prevalence criterion only, it is believed that the foods which were placed in groups 2, 3 and 4 could be included in a global priority list of food allergens based on the fact they affect a substantial proportion of individuals across the world. In addition, prevalence of pecan allergy has been assessed as very low but would need to be on the list because of its homology and concordance of clinical allergy with walnut, which has been reported to have a low prevalence worldwide.

TABLE 5 **SUMMARY OF OVERALL PREVALENCE CATEGORIES OF COELIAC DISEASE AND NON-IGE-MEDIATED FOOD ALLERGY BY INCRIMINATED FOOD**

FOOD	PREVALENCE GROUP				
	0	1	2	3	4
	INSUFFICIENT DATA TO DETERMINE LOW OR HIGH	VERY LOW	LOW	MIXED	HIGH
Animal food allergens					
Cow's milk					
Hen's egg					
Fish (as codfish)					
Crustacean shellfish					
Molluscan shellfish					
Plant-derived foods					
Wheat – Coeliac disease					
Wheat – IgE-mediated food allergy					
Barley – IgE-mediated food					
Rye – IgE-mediated food					
Oats – IgE-mediated food					
Fruits and vegetables					
Celery					
Kiwi					
Lupin					
Legumes					
Peanut					
Soybean					
Seeds					
Buckwheat					
Mustard					
Sesame					
Tree nuts					
Almond					
Coconut					
Brazil nut					
Cashew nut					
Hazelnut					
Macadamia nut					
Pecan [needs to be on the list because of homology with walnut]					
Pistachio					
Pine nut					
Walnut					

The details of prevalence evidence assessments is included in **Annex 3**.

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CHAPTER 4
POTENCY CRITERIA ASSESSMENT OF ALLERGENS

4.1 BACKGROUND AND INTRODUCTION

The Codex General Standard for the Labelling of Prepackaged Foods (GSLPF) (FAO and WHO, 2018) currently mandates that eight foods and ingredients known to cause hypersensitivity shall always be declared, namely cereals containing gluten, crustacea, egg, fish, peanut and soybean, milk and tree nuts. Sulphites (where present at concentrations of ≥ 10 mg/kg) must also be declared. Among criteria for determining this list of priority food allergens, confirmation of allergenicity with a double-blind, placebo-controlled food challenge (DBPCFC) was considered. More recently and in accordance with Joint FAO/WHO Expert Committee on Food Additives (JECFA) guidelines, "The existence of a credible cause-effect relationship, based upon positive DBPCFC or unequivocal reports of reactions with typical features of severe allergic or intolerance reactions" has been used for describing the potency criteria (The Canadian Criteria for the Establishment of New Priority Food Allergens) (Canada and Health Canada, 2011). However, "the existence of a credible cause-effect relationship, based upon positive DBPCFC or unequivocal reports of reactions with typical features of severe allergic or intolerance reactions" has been reported for almost all current and proposed priority allergenic foods.

Therefore, the working group defined the potency criteria for evaluation of IgE-mediated food allergy as follows:

> A value or parameter derived from the existence of a biologically plausible relationship between the amount of protein from an allergenic food ingested and the proportion of the allergic population at risk of responding to that allergen. This relationship could be described using dose distribution modelling of data based upon positive oral food-challenge data from escalating dose studies, preferably using DBPCFC.

4.2 METHODS

The working group considered the outputs from the reviews undertaken, and then categorized allergenic foods into the following three categories or bins (Table 6).

TABLE 6 **CRITERIA DECISION FOR INCLUSION ON GLOBAL PRIORITY ALLERGEN LIST**

	BIN 1	BIN 2	BIN 3
POTENCY	Low	Medium	High

Supporting information

Information recorded or summarized, when available, included the ED10[1] and ED50 from dose distribution modelling, a summary of the data sources, the amount of data available for dose distribution modelling, and the potential for biases that might affect the population-based eliciting dose (EDp) values, as indicated in summary Table 7 for each of the food allergens.

TABLE 7 **TEMPLATE USED TO SUMMARIZE SUPPORTING INFORMATION FOR INDIVIDUAL FOODS**

POTENCY	BIN 1	BIN 2	BIN 3	BIN 4
ED10 MG RANGE, INCLUDING 95% CI	> 100 mg protein	10–100 mg protein	1–10 mg protein	< 1.0 mg protein
ED50 MG RANGE, INCLUDING 95% CI	> 1 000 mg protein	100–1 000 mg protein	10–100 mg protein	< 10 mg protein

SUMMARY OF DATA SOURCES AND ORIGINS (DEMOGRAPHIC, MEDICAL/CLINICAL, GEOGRAPHIC)	
NUMBER OF STUDIES AVAILABLE	n =
NUMBER OF INDIVIDUAL DATA POINTS AVAILABLE	n =

POTENCY		BIN 1	BIN 2	BIN 3
ED10 MG RANGE, POTENTIAL BIASES OF DATA AVAILABLE		High	Adequate	Low
QUANTITY OF DATA AVAILABLE FOR DOSE-DISTRIBUTION MODELLING	not available (n =)	Poor (n ≤ 40)	Adequate (n = ~40 – 100)	Good (n > 100)

[1] Eliciting Dose (EDp) refers to the proportion (p) of the allergic population predicted by dose distribution modelling to react to a specified amount (dose) of total allergenic protein in a food. Thus, ED10 and ED50 refer to the doses predicted to provoke reactions in 10 percent and 50 percent of the allergic population respectively.

4.2.1 PRINCIPLES OF DATA SELECTION AND ANALYSIS OF DOSE DISTRIBUTIONS FOR ALLERGENIC POTENCY – SUMMARY

Criteria for selection and inclusion for subject data point, as well as extraction of individual No observed effect levels (NOAELs) and Lowest observed effect levels (LOAELs), together with Interval-censoring analysis (Icsa) of such data were first described in detail for peanut data in Taylor *et al.* (2009). They were developed and refined further, most recently with the publication of Westerhout *et al.* (2019) defining in detail the objective symptoms which form the foundation of the analysis, as well as how NOAELs and LOAELs are extracted from DBPCFC data. Statistical methods for application of Icsa in food allergen dose distribution modelling were updated by Wheeler *et al.* (2021) to include model averaging and account for study-to-study heterogeneity. Applying these criteria, generation of dose distributions and subsequent derivation of discrete or cumulative EDp values is described for challenge data on 14 allergenic foods in Remington *et al.* (2020) and Houben *et al.* (2020).

Westerhout *et al.* (2019) also reported the selection criteria of studies reporting individual food challenge data:

> *In short, data from DBPCFCs were included if they started at low doses (< 1 mg ideal, with < 10 mg or < 100 mg also used with exceptions depending on the type of allergen and amount of available data) and if the authors/clinics clearly reported the dosing scheme used, indicated if/when repeated doses were used, detailed the challenge material and reported the symptoms in an individual fashion or reported a grouped symptom classification with a clear separation between objective and subjective symptoms. Additionally, data were included from study protocols using different time intervals between doses (15-30 minutes on average, up to 2 hours between doses). Publications were also used if some but not all reported individuals had data available in the desired format. Due to some extremely high dose labial challenges, DBPCFCs starting with a positive labial challenge were excluded, and protocols beginning with labial challenges were discouraged unless the exact labial dose could be verified and it could be safely assumed that the labial dose was smaller than the following ingested doses. Naturally, in contrast to the inclusion criteria, additional general exclusion criteria included results from DBPCFCs with extremely high starting doses, if the full dosing scheme was not able to be derived from reported information, if objective and subjective symptoms were unable to be separated from reported grouped symptoms, and if the challenge material or protein content could not be derived from the reported information. Additionally, data from individuals in food-challenge datasets who do not react to any dose during challenge and were determined to be tolerant were excluded from further threshold determinations for population risk assessment* (Westerhout *et al.*, 2019).

As detailed in Remington *et al.* (2020) and Houben *et al*. (2020), the authors used the criteria from Westerhout *et al.* (2019) to systematically search and update their publication database with results identified in databases such as PubMed and Scopus with the general search terms: "(allergy AND [food OR nutrition] AND [DBPCFC OR challenge OR provocation OR threshold OR eliciting])". Publications with potential potency data were also added from a list of all publications relevant to food allergy as identified during custom screening of Current Contents (TM), other literature databases such as Medline, scanning content pages of specialty allergy journals, and cross-referencing of bibliographies of publications. Publications up to 2011 were identified, detailed and included in the analysis of Taylor *et al.* (2014). The database was further updated with publications between 2011–2018, with over 2 516 titles and abstracts screened for further review, 570 peer-reviewed articles kept for full PDF review, and 47 identified as containing quantitative individual level data in a useable format, as detailed and included in the analysis of Remington *et al.* (2020) and Houben *et al.* (2020).

For the current potency criteria review, the Subgroup of the Expert Committee for Potency reviewed the dose distributions as detailed in Remington *et al.* (2020) and Houben *et al.* (2020), as well as 71 publications identified by the Subgroup to potentially contain general group-level potency data (but previously identified not to contain detailed individual level data – and not included in the Houben *et al.* (2020) dose distributions). For additional details, please see the main text of Report 2, as well as its Annex for the 71 studies considered. These studies were identified after applying similar search criteria, abstract screening of nearly 3 000 publications, and a PDF review of more than 450 publications identified for detailed review. Furthermore, the Subgroup reviewed additional studies identified for potential potency review by members of the current working group.

4.2.2 SYMPTOMS CONSIDERED IN ASSESSMENT AND DERIVATION OF NOAELS/LOAELS

The Subgroup considered data based on objective symptoms resulting from oral food challenges in allergic individuals. Objective symptoms include any symptom that is externally observable, while subjective symptoms cannot be confirmed by clinical observers (see **Table 8** for a list of possible symptoms). While **Table 8** is a broad list of symptoms, it should be acknowledged that it is not an exhaustive list, and other recorded subjective or objective symptoms are also possible. Again, any dose distributions, EDp values, or individual NOAELs and LOAELs reviewed in this report were considered if it was clear that the data reported referred to objective symptoms.

TABLE 8 **MOST COMMON SIGNS AND SYMPTOMS OF ALLERGIC REACTIONS TO FOOD, AS REPORTED IN PUBLICATIONS AND UNPUBLISHED CLINICAL DATA**

SUBJECTIVE SYMPTOMS	OBJECTIVE SYMPTOMS
Oral cavity	
> Pruritus (itching) and paresthesia (tingling sensation) of the oral cavity, pharynx and/or lips (so called oral allergy symptoms [OAS])	> Lip swelling > Redness/swelling of the oral mucosa > Blisters of the oral mucosa
Skin	
> Pruritus (itching)	> Urticaria > Angioedema > Flush > Erythema (Redness)
Eyes and Nose	
> Pruritus (itching)	> Red eye/conjunctival hyperemia > Tearing > Sneezing > Rhinorrhea
Gastrointestinal	
> Dysphagia > Abdominal/gastric pain* > Cramps > Nausea > Bloating	> Diarrhea > Vomiting**
Neurological	
> Headache > Dizziness > Anxiety > Tension/agitation	> Seizures
Respiratory	
> Laryngeal/throat tightness > Thoracic/chest tightness > Dyspnea/shortness of breath	> Laryngeal edema > Dysphonia > Wheezing > Reduced peak expiratory flow/drop in FEV1 > Silence (in lung auscultation) > Breathless to speak > Rapid breath > Chest retractions > Cough
Cardiovascular	
> Faintness > Tiredness	> Change in heart rate/tachycardia > Hypotension/drop of blood pressure > Change in consciousness
Other	
> Uterine cramps/contractions	

*Abdominal pain and gastric pain are considered objective symptoms provided they are observed in children less than three years old.

**Vomiting is not considered an objective symptom in children less than one year of age unless the clinician stops the challenge because of vomiting. If vomiting occurs at the final dose of the challenge, it is not considered an objective symptom in children less than one year old, unless additional objective symptoms are present.

Source: Adapted from Westerhout *et al.*, 2019

Selection criteria of studies reporting individual food challenge data, where similar criteria were followed by this Subgroup, are reported by Westerhout *et al.* (2019):

> *As a subject is challenged with increasing doses during a DBPCFC, objective symptoms occur and that specific dose is designated as the lowest observed adverse effect level (LOAEL). The highest dose that does not lead to objective symptoms (e.g. the immediately preceding step in the progression) is then designated the no observed adverse effect level (NOAEL). The exact doses (mg) of total protein for individual subjects' NOAELs and LOAELs were established based on the dosing scheme and challenge material form as provided in the publication/clinic (e.g. scrambled whole egg, scrambled egg white, whole egg powder, egg white powder). Individual NOAELs and LOAELs were also derived from summarized group data when only objective symptoms were included in the results and the number of subjects was clearly stated. In case of ambiguity regarding reported symptom data in the publications of interest, the corresponding author of a publication or the responsible clinician was contacted by the researchers for further details. When the challenge doses were reported in amounts of allergenic food they were converted to mg of total protein of the allergenic food as previously described by Taylor et al. All individual NOAELs and LOAELs were expressed in terms of doses (mg) of total protein of the allergenic food.*
>
> *There are two ways of expressing NOAELs and LOAELs, either in discrete or cumulative fashion. Discrete values represent the protein amount for each individual dose in the challenge scheme, either NOAEL or LOAEL, irrespective of all previous doses ingested during the food challenge. In contrast, cumulative NOAELs and LOAELs take into account the amount of protein of all the preceding doses in the challenge as well. For example, a simple 4-step dosing scheme with discrete doses of 1, 3, 10, and 30 mg protein would be reported as cumulative doses of 1, 4, 14, and 44 mg protein. One might assume that a dose-response curve based on discrete doses would be more conservative than when utilizing cumulative doses, but in practice there is little observed difference between the discrete or cumulative EDp values predicted to cause reactions in 1% or 5% of the allergic population. Additionally, due to differences in the shape and scale of the calculated parametric dose distribution models fitted to discrete or cumulative data points, curves with steeper slopes can lead to predicted discrete population EDp values that are actually slightly higher than the cumulative population EDp values in the risk management dosing range of interest (e.g.ED01, ED05, lower 95% confidence interval of the ED05 – the mg protein amount predicted to cause reactions in 1% or 5% of the allergic population). However, differences can occur at higher EDp values such as the ED50, so the risk management goal should be considered when choosing discrete or cumulative reporting units. For the purposes of this study, a distinction between discrete and cumulative reporting units is made when necessary but it is not the main focus of the study.*

> *Additionally, there are two different endpoints that should be considered when interpreting data from food challenges: clear clinical challenge stopping criteria vs the LOAEL for risk assessment and risk management purposes. Confirming the presence of a clinical food allergy is of extreme importance to a clinician and the potentially allergic patient, due to the significant impact food allergy avoidance has on day-to-day life. Thus, situations can arise where challenges are continued after the first appearance of symptoms, either subjective or objective, until clear challenge stopping criteria (or protocol-defined stopping criteria) have been met and the allergy is confirmed. In these cases, the clinical challenge stopping dose may be different than the determined LOAEL for population risk assessment and risk management purposes. Situations of this nature can include, but are not limited to: transient objective symptoms, objective symptoms continuing from dose to dose, one or multiple doses between objective symptoms and a lack of objective symptoms* (Westerhout *et al.*, 2019).

When sufficiently detailed information was available and when it was indicated that challenges were continued after the first appearance of symptoms, the NOAEL/LOAEL for risk assessment and risk management purposes was determined using the criteria outlined by Westerhout *et al.* (2019).

Assessment of bias

We attempted to provide a qualitative estimate of whether the EDp estimates could be biased, starting from the goal of identifying global priority allergenic foods and ingredients. Thus, studies limited to a small number of regions, or even confined to limited parts of wider regions (e.g. data from celery studies being confined to Central Europe) would lead to a conclusion of potentially high bias. Other factors included whether studies were limited to a particular fraction of the population (e.g. children) or where inclusion criteria could plausibly have led to a more (or less) sensitive population being tested (e.g. immunotherapy studies). Finally, factors inherent in the study design or results which could affect the shape of dose-distributions, such as a high proportion of left- or right-censored results, also contributed to our overall judgement.

4.3 RESULTS

4.3.1 OUTCOMES – CONSENSUS OPINION OF THE SUBGROUP OF THE EXPERT COMMITTEE FOR POTENCY

The Subgroup of the Expert Committee for Potency reached consensus on the level of potency for food allergens and these are summarized in **Table 9**.

TABLE 9 THE OUTCOME FROM THE SUBGROUP OF THE EXPERT COMMITTEE FOR POTENCY

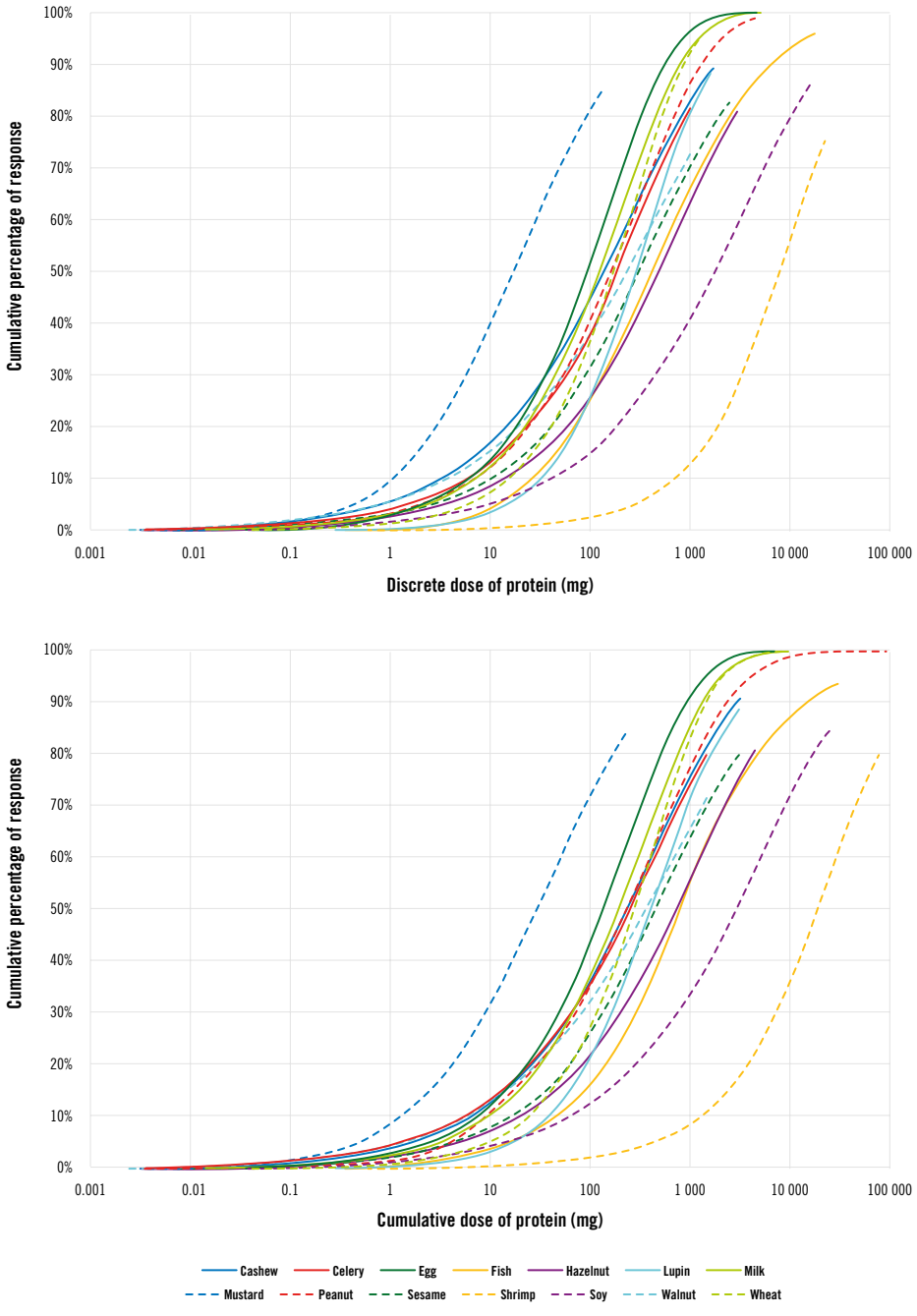
ALLERGEN	POTENCY
Milk	Medium
Egg	Medium
Peanut	Medium
Hazelnuts	Medium
Cashew nuts	Medium
Crustacean	Low (shrimp); N/A for others in group
Wheat – IgE	Medium
Fish	Medium
Walnuts	Medium
Sesame	Medium
Pistachio	N/A (cross with cashew)
Pecan nuts	N/A (cross with walnut)
Mustard	High
Soybean	Medium/Low
Lupin	Medium
Brazil nut	N/A
Almond	N/A
Other cereals	N/A
Kiwi	N/A
Pine nuts	N/A
Molluscan shellfish	N/A
Coconut	N/A
Chestnuts	N/A
Celery	Medium
Macadamia	N/A
Buckwheat	N/A

The detail of potency evidence assessments is included in **Annex 4**.

4.3.2 DOSE DISTRIBUTION INFORMATION

The dose distribution curves for 14 allergenic foods available from Houben *et al.* (2020) are reprinted here as **Figure 4**.

FIGURE 4. **EDP CURVES FROM THE MODEL AVERAGED POPULATION THRESHOLD DOSE DISTRIBUTIONS FOR 14 PRIORITY ALLERGENIC FOODS, BASED ON DISCRETE (UPPER GRAPHS) AND CUMULATIVE (LOWER GRAPHS) DOSE DATASETS. DOSES ARE EXPRESSED IN MG TOTAL PROTEIN FROM THE ALLERGENIC FOOD**



Source: Adapted from Houben *et al.*, 2020.

As seen in **Figure 4**, the dose distribution intervals for the majority of these 14 allergenic foods in Houben *et al.* (2020) were clustered in a similar range, with their respective EDp estimates and corresponding 95 percent confidence intervals spanning bins 2 and 3, with the exception of mustard, soy and shrimp (see **Annex 4** "Potency criteria decision and supporting information for individual foods" for more detailed information). The summary tables in **Annex 4** were used to facilitate the discussion during this first meeting with regards to the potency criteria decision and the overall priority list. This led to the following potency criteria designations for the 14 foods:

> **High:** mustard

> **Medium:** wheat, celery, milk, fish, peanut, lupin, buckwheat, egg, sesame, hazelnut, walnut (pecan), cashew (pistachio)

> **Medium/Low:** soy

> **Low:** shrimp (crustacea)

> **Insufficient data for dose-distribution modelling:** other cereals, buckwheat, kiwi, brazil nut, macadamia, pistachio (but cross-react with cashew), almond, chestnuts, pecan nuts (but cross-react with walnuts), pine nuts, coconut and molluscan shellfish

However, it should be noted that the 95 percent confidence intervals for one or both the mustard ED10 and ED50 estimates overlap with the 95 percent confidence intervals for cashew, celery, egg, hazelnut, lupin, milk, peanut, sesame, walnut and wheat. Thus, while the potency decision is labelled as "high" for mustard, there is a large level of overlap of EDp estimates between mustard and the foods designated "medium" potency.

Additionally for the current potency criteria review, the Subgroup reviewed the dose distributions as detailed in Remington *et al.* (2020) and Houben *et al.* (2020), as well as 71 publications identified by the Subgroup to potentially contain general group-level potency data (but previously identified not to contain detailed individual level data – and not included in the Houben *et al.* (2020) dose distributions). From these 71 publications (Food and number of studies identified [Peanut 22, Cow's milk 15, Egg 14, Wheat 5, Soybean 3, Cashew 3, Hazelnut 3, Walnut 1, Buckwheat 1, Pecan 1, Apple 1, Peach 1, and Yellow Pea 1]), no information was found that altered the potency designation assigned above.

Finally, these same data sources will be further discussed and used for the second meeting and reporting of potential thresholds/reference doses. For additional information, please see the main text of Report 2, as well as its Annex.

4.4. REFERENCES

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CHAPTER 5
SEVERITY ASSESSMENT OF PRIORITY ALLERGENS

5.1 BACKGROUND

As outlined above, there are different severity considerations for IgE-mediated vs non-IgE-mediated food allergy and coeliac disease. The former can manifest as acute anaphylaxis, a "serious systemic hypersensitivity reaction that is usually rapid in onset and may cause death" (Cardona *et al.*, 2020). In contrast, the latter are very rarely associated with acute life-threatening presentations. For the purpose of prioritizing food allergens on the basis of public health importance, it is therefore reasonable to propose that severity considerations could be mostly informed by the relative roles of different allergens in causing anaphylaxis in at-risk individuals (while acknowledging the risks of gluten exposure in patients with coeliac disease).

The Codex currently requires disclosure in prepackaged foods for ingredients relating to eight food groups: cereals containing gluten, crustacea, egg, fish, peanut and soybean, milk and tree nuts; sulphites (where present at concentrations of ≥ 10 mg/kg) must also be declared.[2] Among criteria for determining this list of priority food allergens, the Codex stated that "there should be reports of severe systemic reactions following exposure to the foodstuff." However, severe systemic (allergic) reactions (often termed anaphylaxis) have been reported to almost all foods.

There are limited data or criteria relating to the relative frequencies or rates of anaphylaxis needed to determine a priority food allergen.[3] The data are also impacted by significant geographical differences in dietary consumption patterns and behaviors, which also affect the prevalence of allergen-specific food allergies worldwide. As a result, some countries and regions reference specific food allergens in local legislation which are not in the Codex list as priority allergens.

[2] While hypersensitivity reactions to sulphite exposure from foods have been reported, sulphite do not cause IgE- or immune-mediated reactions and are thus excluded from this assessment.

[3] While the current priority allergens are in general considered to cause 90 percent of food allergies (and food-induced allergic reactions), there are no established global criteria for assessing food allergen severity in determining the Codex list of food allergens and other priority allergens.

In assessing the relevance of severity when evaluating food allergens for inclusion on a priority list, there are several factors to consider. First and foremost, there are no established biomarkers for food allergen severity. As a result, severity is a clinical assessment which must be inferred from published or other documented evidence of food-induced allergic reactions and related adverse health consequences observed within population(s) of allergic individuals (Turner *et al.*, 2016). This evidence is confounded by differences in definitions of severity and the accuracy of reporting.[3] Furthermore, while anaphylaxis is accepted as a serious allergic reaction, the majority of anaphylaxis reactions are resolved without intervention; thus, "anaphylaxis" alone presents an incomplete assessment of severity.[4] One severity endpoint for which there is a consensus with respect to severity are those reactions that result in near-fatal or fatal anaphylaxis; these occur at an annual incidence of around 1 in 10 000 for food allergic individuals (Vyas *et al.*, 2016). Most (but not all) of the priority food allergens identified by the Codex have been associated with fatalities.

While there are increasing data globally relating to the relative prevalence of food allergy due to specific foods, these epidemiological data may not correspond to the list of foods which commonly cause anaphylaxis. As such, there has been no global survey assessing geographical differences in the relative proportions of anaphylaxis due to specific food triggers. Prevalence data should ideally be derived from unselected populations; however, this often results in very small numbers of individuals allergic to a specific food and thus a high level of uncertainty over the resulting estimate for prevalence.

As part of preparation for this Codex activity, Baseggio Conrado (2021) undertook a systematic review of the literature to identify studies reporting proportions of anaphylaxis in different countries and regions due to specific food triggers (**Table 10**). The search strategy is described in the manuscript and includes all studies where details were provided as to specific triggers for food anaphylaxis, either presenting to a medical facility or reported to a central registry. This allows a relative proportion of anaphylaxis cases due to a particular food allergen to be calculated. Case series reporting more than ten fatalities due to food anaphylaxis were also included.

5.2 METHODS

The working group considered the outputs from the systematic review undertaken and then categorized allergens into the following groups:

> Allergens which cause at least 5–10 percent of anaphylaxis reactions in three or more Codex regions

> Allergens which are considered to cause at least 5–10 percent of anaphylaxis reactions in only one or two Codex regions

[4] For example, some reactions that meet some definitions of anaphylaxis are relatively self-limited and not associated with adverse health consequences, while other reactions that are arguably life threatening do not meet some definitions, despite the severity resulting in prolonged hospitalization.

- (i) Allergens which cause a lower proportion of anaphylaxis reactions in all regions ***OR***
- (ii) Allergens which cause at least 5–10 percent of anaphylaxis reactions in only one CODEX region, but a lower proportion of anaphylaxis reactions elsewhere

Initial assignment was based on **Table 10**, but then included a consideration of the quality of other evidence relating to food allergy severity endpoints and a consensus decision was reached. An assessment of the evidence justifying the above categorization was also made for each allergen:

> Level 1: High level of confidence by the working group in the estimate of the proportion of anaphylaxis reactions due to a given food allergen (and thus further data is unlikely to substantially change confidence in this estimate).

> Level 2: Lower confidence that the available data indicates that a given allergen causes at least 5–10 percent of anaphylaxis reactions, and thus other evidence relating to fatal food anaphylaxis, allergen cross-reactivity and/or expert judgement required."

TABLE 10 **GLOBAL HEAT MAP OF COMMON FOOD ALLERGENS REPORTED TO CAUSE ANAPHYLAXIS, BY CODEX REGION AND COUNTRY/AREA**

	PEANUT	TREE NUTS	SESAME	WHEAT	HEN'S EGG	COW'S MILK	CELERY	CRUSTACEA	MOLLUSCA	FISH	SOYBEAN	LUPINE	OTHER LEGUMES	FRUIT	BUCKWHEAT
CODEX	✓	✓		✓	✓	✓		✓		✓	✓				
AFRICA															
Morocco	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
South Africa	✓	✓		✓	✓	✓		✓	✓	✓	✓				
ASIA															
China	✓	✓		✓	✓	✓		✓		✓	✓				
China, Hong Kong Special Administrative Region	✓	✓		✓	✓	✓		✓		✓	✓				
Japan	✓	(✓)		✓	✓	✓		✓		(✓)	(✓)			(✓)	✓
Republic of Korea	✓	(✓)		✓	✓	✓		✓	(✓)	✓	✓				✓
Pakistan															
Philippines	✓	✓		✓	✓	✓		✓		✓	✓				
Singapore	✓	✓		✓	✓	✓		✓		✓	✓				
Sri Lanka															
Thailand	✓	✓		✓	✓	✓		✓		✓	✓				
EUROPE															
EU Member States	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Israel															
Russian Federation															
Switzerland	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
Turkey	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
United Kingdom of Great Britain and Northern Ireland	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓			
LATIN AMERICA/CARIBBEAN (LAC)															
Argentina	✓	✓		✓	✓	✓		✓		✓	✓				
Brazil	✓	✓		✓	✓	✓		✓		✓	✓				
Chile	✓	✓		✓	✓	✓		✓		✓	✓				
Mexico	✓	✓		✓	✓	✓		✓		✓	✓				
Venezuela (Bolivarian Republic of)	✓	✓		✓	✓	✓		✓		✓	✓				
NEAR EAST															
Iran (Islamic Republic of)															
Qatar	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓			
Saudi Arabia	✓	✓	✓	✓	✓	✓		✓		✓	✓	✓			
Tunisia															
NORTH AMERICA/SW PACIFIC (NASWP)															
Australia	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓			
Canada	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓				
New Zealand	✓	✓	✓	✓	✓	✓		✓	✓	✓	✓	✓			
United States of America	✓	✓	(✓)	✓	✓	✓		✓		✓	✓				

'✓' indicates local legislation requiring disclosure for that allergen; (✓) indicates more limited or voluntary disclosure recommended. Heat map colours indicate relative (rather than absolute) prevalence of that allergen (group) as a common cause of food anaphylaxis in that region/country/area.

Source: Adapted and reproduced with permission from Baseggio Conrado *et al.*, 2021.

5.3 CONSENSUS OPINION OF THE SUBGROUP OF THE EXPERT COMMITTEE FOR SEVERITY

The Subgroup of the Expert Committee for Severity reached consensus on the severity of allergic reactions associated with food allergens and these are summarized in **Table 11**.

TABLE 11 **THE OUTCOME FROM THE SUBGROUP OF THE EXPERT COMMITTEE FOR SEVERITY**

GROUP C (I) Lower proportion of anaphylaxis, all regions	GROUP C (II) Higher proportion of anaphylaxis, 1 region	GROUP B Higher proportion of anaphylaxis, 1–2 regions	GROUP A Higher proportion of anaphylaxis, 3+ regions
			PEANUT
Tree nuts >Shea nut		Tree nuts >Pine nuts[a] >Macadamia[b]	Tree nuts >**WALNUT**, Pecan[c] >**CASHEW**, **PISTACHIO** >**HAZELNUT** >**ALMOND** >Brazil nut[d]
Coconut			
			Sesame[e]
	Mustard (France)		
			WHEAT[f]
	BUCKWHEAT		
	CELERY		
			EGG
			COW'S MILK (+ other mammalian milk)[g]
			FISH
			CRUSTACEA
	Mollusca		
		Lupin[h]	
SOYA[i]			
Fruits >Other fruits[j]	Fruits >Peach[j]		

CAPITALS: level one evidence; Normal font: level two evidence.

Notes:
[a] Evidence of being a trigger for anaphylaxis in two regions, but lower-level prevalence.
[b] Trigger for anaphylaxis in two regions, unknown prevalence.
[c] On basis of cross-reactivity with walnut (high level evidence).
[d] Brazil nut implicated in several fatalities.
[e] Included as priority allergen on basis of fatality data.
[f] Consensus that wheat should be a priority allergen as a common trigger for non-IgE-mediated food allergy.
[g] Included on basis of cross-reactivity to cow's milk.
[h] No significant signal currently, but this may be related to low levels of inclusion as an ingredient due to concerns over cross-reactivity to peanut.
[i] Placed in low-priority list, as few fatalities reported in last 20 years and low severity signal.
[j] Not included as a priority allergen as fruit is unlikely to be consumed as an unidentified ingredient in processed foods.

Watch list

The Subgroup highlighted the following allergens which may cause increasing cases of anaphylaxis as their use in food production changes/increases in **Table 12**.

TABLE 12 **THE WATCH LIST FROM THE SUBGROUP OF THE EXPERT COMMITTEE FOR SEVERITY**

> Legumes > Pea (protein concentrates) > Lentils > Chickpeas > Non wheat, gluten-containing grains > Buckwheat	> Seeds > Sunflower > Poppy seed > Cottonseed > (Green) Kiwifruit > Alpha-gal (red meat)

5.4. REFERENCES

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CHAPTER 6
SENSITIVITY ANALYSIS FOR THE CRITERIA WEIGHTS AND INVESTIGATED BINNING PREVALENCE

6.1 METHODS

Hazard prioritization is a well-known part of the risk assessment and risk management process (FAO and WHO, 2013, 2014). The prioritization process was adapted to the three criteria previously detailed (prevalence, potency, severity) for IgE-mediated food allergies as a means to help guide the discussion and decision-making process for which foods should be listed as global priority allergens. The defined criteria, binning and prioritization process provides transparency and repeatability of the assessment when re-evaluation of new foods or new data is deemed necessary.

The Subgroup of the Expert Committee for Prevalence defined global criteria for evaluating the foods to be listed as global priority allergens, with the process comprising the following general steps (FAO and WHO, 2013):

- **Step 1.** Identification of the foods to be evaluated
- **Step 2.** Identification and definition of the criteria by which each selected food would be quantified
- **Step 3.** Assignment of criterion-based values to the foods (detailed in sections 3, 4 and 5)
- **Step 4.** Normalization of these values to make them comparable between criteria
- **Step 5.** Weighting of the criteria to reflect their relative importance

> **Step 6.** Combining the weighted normalized values for each food to produce a score and repeating the process for the combinations of weighting and binning options

> **Step 7.** Plotting of the scores to help guide discussion of which foods should be listed as global priority allergens

6.1.1 PREVALENCE IN THREE BINS

Criteria were binned with a normalizing value as follows. Due to a potentially differing number of bins for the prevalence criteria when compared to potency and severity, the option of the prevalence criteria being normalized across three or four bins was investigated.

When the prevalence criterion is normalized across three bins, the result of "insufficient data" and "very low" both receive score of 0, as shown in **Table 13**.

TABLE 13 **PREVALENCE IN THREE BINS**

	CRITERIA	BIN 0	BIN 1	BIN 2	BIN 3	BIN 4
NORMALIZED VALUE	**Normalizing option (Potency/Severity)**	0		0.33	0.66	1
	Normalizing option 1 (Prevalence)	0	0	0.33	0.66	1

	CRITERIA	BIN 0	BIN 1	BIN 2	BIN 3	BIN 4
POTENCY	**Potency for matrix**	Insufficient data (N/A)		Low	Medium	High
PREVALENCE	**Prevalence (single combined estimate)**	Insufficient data (N/A)	Very low	Low	Mixed	High
			< 0.5% in one region only OR < 0.1% in all regions	< 0.5% in all regions	> 1% in one region AND 0.5–1.0% in at least one other region	> 1.0% in more than one region
SEVERITY	**Severity (single combined estimate)**	Insufficient data (N/A)		Lower proportion of anaphylaxis, all regions OR Higher proportion of anaphylaxis, 1 region	Higher proportion of anaphylaxis, 1–2 regions	Higher proportion of anaphylaxis, 3+ regions
				C1/C2	B	A

Note. The grey boxes indicate when a bin does not apply for the specific criteria.

6.1.2 PREVALENCE IN FOUR BINS

When the prevalence criterion is normalized across four bins, there is a separation of "insufficient data" and "very low" results which indicates when data are available, but prevalence is very low (**Table 14**).

TABLE 14 **PREVALENCE IN FOUR BINS**

	CRITERIA	BIN 0	BIN 1	BIN 2	BIN 3	BIN 4
NORMALIZED VALUE	**Normalizing option (Potency/Severity)**	0		0.33	0.66	1
	Normalizing option 2 (Prevalence)	0	0.25	0.5	0.75	1

	CRITERIA	BIN 0	BIN 1	BIN 2	BIN 3	BIN 4
POTENCY	**Potency for matrix**	Insufficient data (N/A)		Low	Medium	High
PREVALENCE	**Prevalence (single combined estimate)**	Insufficient data (N/A)	Very low	Low	Mixed	High
			< 0.5% in one region only OR < 0.1% in all regions	< 0.5% in all regions	> 1% in one region AND 0.5–1.0% in at least one other region	> 1.0% in more than one region
SEVERITY	**Severity (single combined estimate)**	Insufficient data (N/A)		Lower proportion of anaphylaxis, all regions OR Higher proportion of anaphylaxis, 1 region	Higher proportion of anaphylaxis, 1–2 regions	Higher proportion of anaphylaxis, 3+ regions
				C1/C2	B	A

Note. The grey boxes indicate when a bin does not apply for the specific criteria.

6.1.3 EIGHT DIFFERENT WEIGHTS USED FOR POTENCY, PREVALENCE AND SEVERITY CRITERIA AS A CHECK FOR SENSITIVITY TO DIFFERENT WEIGHTING VALUES

As different risk assessors or risk managers could choose to weight the three criteria in slightly different fashions, eight (8) different weighting options were investigated based on inputs from the Subgroup of the Expert Committee for Prevalence in this consultation (**Table 15**).

TABLE 15 **EIGHT DIFFERENT WEIGHTS USED FOR POTENCY, PREVALENCE AND SEVERITY**

	EQUAL WEIGHT	WEIGHT OPTION 2	WEIGHT OPTION 3	WEIGHT OPTION 4	WEIGHT OPTION 5	WEIGHT OPTION 6	WEIGHT OPTION 7	WEIGHT OPTION 8
POTENCY	0.33	0.4	0.3	0.3	0.2	0.1	0.15	0.15
PREVALENCE	0.33	0.3	0.4	0.3	0.4	0.45	0.5	0.6
SEVERITY	0.33	0.3	0.3	0.4	0.4	0.45	0.35	0.25

6.1.4 CALCULATION

For each food, the weighted normalized values were combined as follows to obtain a score:

> Score (priority number) = (C1*W1) + (C2*W2) + (C3*W3)

> Score (priority number) = (Potency_binning * Potency_weight) + (Prevalence_binning * Prevalence_weight) + (Severity_binning * Severity_weight)

Example Milk (equal weight for all criteria) (**Table 16**):

> Score (milk – equal weight) = (0.66 * 0.33) + (1 * 0.33) + (1 * 0.33) = 0.8778

TABLE 16 **EXAMPLE OF THE CALCULATION FOR MILK**

ALLERGEN	POTENCY	PREVALENCE	SEVERITY	POTENCY	PREVALENCE	SEVERITY	SCORE – EQUAL WEIGHT
Milk	Medium	High	Higher proportion of anaphylaxis, 3+ regions	0.66	1	1	0.8778

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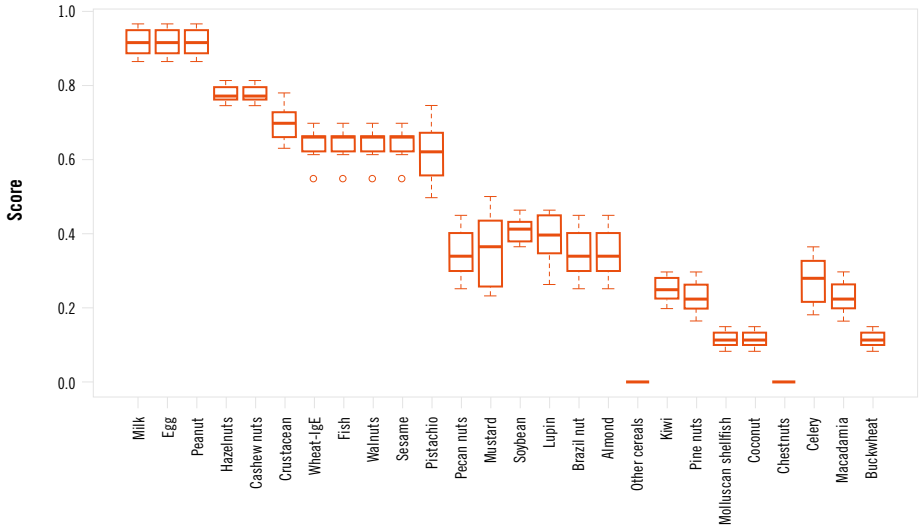
6.2 RESULTS

6.2.1 SENSITIVITY

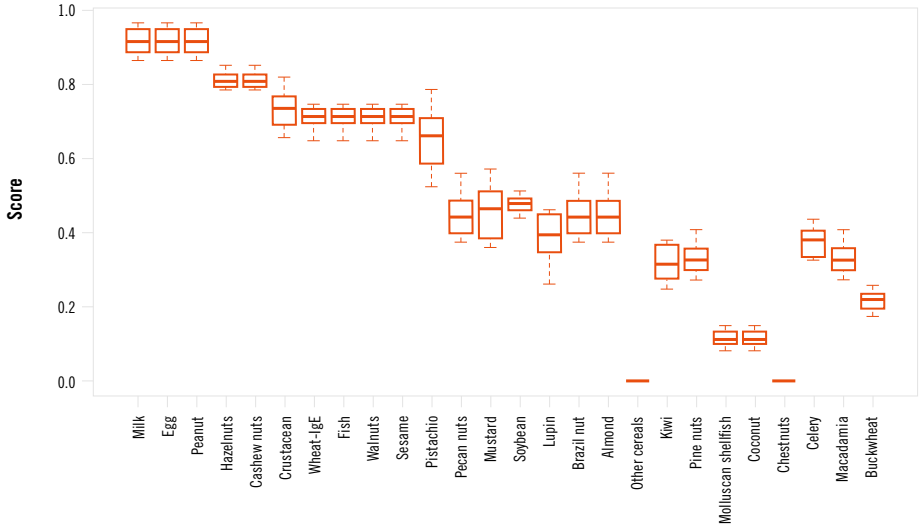
The results of combining the weighted normalized values for each food, for all combinations of eight weighting options and the two different binning options for the prevalence criteria are shown in **Figure 5** and **Figure 6** .

FIGURE 5. **SENSITIVITY IN THREE BINS**



Source: Authors' own elaboration.

FIGURE 6. **SENSITIVITY IN FOUR BINS**



Source: Authors' own elaboration.

6.2.2 RESULTS

Based on the discussion and consensus from each of the Subgroups for the Expert Committee (prevalence, potency and severity) and the calculation to have the final score of the allergens, the assessed results are in the list below (**Table 17**). The Expert Committee decides that allergens with the score "A" would be in the priority list, and those with a score of "C" will not. The Expert Committee had a discussion on all the "B" listed allergens in the next chapter to decide how to categorize these allergens and reach a conclusion.

TABLE 17 **THE OUTCOME OF THE SENSITIVITY ANALYSIS**

A/B/C	ALLERGEN	POTENCY	PREVALENCE	SEVERITY
A	**Milk**	Medium	High	Higher proportion of anaphylaxis, 3+ regions
A	**Egg**	Medium	High	Higher proportion of anaphylaxis, 3+ regions
A	**Peanut**	Medium	High	Higher proportion of anaphylaxis, 3+ regions
A	**Hazelnuts**	Medium	Mixed	Higher proportion of anaphylaxis, 3+ regions
A	**Cashew nuts**	Medium	Mixed	Higher proportion of anaphylaxis, 3+ regions
A	**Crustacean**	Low (shrimp); N/A for others in group	Mixed	Higher proportion of anaphylaxis, 3+ regions
A	**Wheat – IgE**	Medium	Low	Higher proportion of anaphylaxis, 3+ regions
A	**Fish**	Medium	Low	Higher proportion of anaphylaxis, 3+ regions
A	**Walnuts**	Medium	Low	Higher proportion of anaphylaxis, 3+ regions
A	**Sesame**	Medium	Low	Higher proportion of anaphylaxis, 3+ regions
A - (with cashew)	**Pistachio**	N/A (cross with cashew)	Mixed	Higher proportion of anaphylaxis, 3+ regions
A - (with walnut)	**Pecan nuts**	N/A (cross with walnut)	Very Low	Higher proportion of anaphylaxis, 3+ regions
B - discuss	**Mustard**	High	Very Low	Higher proportion of anaphylaxis, 1 region
B - discuss	**Soybean**	Medium/Low	Low	Lower proportion of anaphylaxis, all regions
B - discuss	**Lupin**	Medium	N/A	Higher proportion of anaphylaxis, 1-2 regions
B - discuss	**Brazil nut**	N/A	Very Low (regional)	Higher proportion of anaphylaxis, 3+ regions
B - discuss	**Almond**	N/A	Very Low	Higher proportion of anaphylaxis, 3+ regions
B - discuss	**Other cereals**	N/A	N/A	N/A
C	**Kiwi**	N/A	Low	Lower proportion of anaphylaxis, all regions
C	**Pine nuts**	N/A	Very Low	Higher proportion of anaphylaxis, 12 regions
C	**Molluscan shellfish**	N/A	N/A	Higher proportion of anaphylaxis, 1 region
C	**Coconut**	N/A	Not done	Lower proportion of anaphylaxis, all regions
C	**Chestnuts**	N/A	Not done	N/A
C - (regional)	**Celery (regional)**	Medium	Very Low (regional)	Higher proportion of anaphylaxis, 1 region
C - (regional)	**Macadamia**	N/A	Very Low (regional)	Higher proportion of anaphylaxis, 1–2 regions
C - (regional)	**Buckwheat**	N/A	Very Low	Higher proportion of anaphylaxis, 1 region

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CHAPTER 7
DISCUSSION ON B LISTED ALLERGENS

7.1 MUSTARD

Mustard includes several botanical species (*Brassica nigra*, *Brassica juncea*, *Brassica hirta* and *Sinapis alba*), which are used as condiments and as ingredients in foods (dressings, sauces, etc). It is a priority allergen in some region or countries (Canada and Europe), as it may be "hidden" in foods, but it is not in the current Codex priority allergen list (Section 4.2.1.4 of General Standards for the Labelling of Prepackaged Food).

Prevalence data based on food challenges for mustard allergy are scarce, and most of the prevalence studies in unselected populations have been published in Europe. A prevalence of 0.03 percent based on a probable diagnosis of mustard allergy has been reported in Poland (grade 2) but not found in five other European countries (Lyons *et al.*, 2019). An overall assessment of prevalence (< 0.5% in one region only OR < 0.1% in all regions) of mustard is very low.

Mustard causes at least 5–10 percent of anaphylaxis reactions in only one Codex region (France), but a lower proportion of anaphylaxis reactions elsewhere. An overall assessment of severity is in group "C", where the severe reactions are found in only one Codex region.

Although the overall assessment of potency is considered as high, the data quantity available is poor (n < 40 individuals). In addition, this result overlaps with the 95 percent confidence intervals for cashew, celery, egg, hazelnut, lupin, milk, peanut, sesame, walnut and wheat. The Expert Committee recommends that mustard not be listed as a global priority allergen but may be kept on a list of allergens for regional consideration.

7.2 SOYBEAN

Soybeans were placed on a list of priority allergenic foods for labelling purposes in 1999 by the Codex Alimentarius Commission. The inclusion of soybean was placed on the list was recommended by a FAO Technical Consultation on Food Allergies held in 1995. The Technical Consultation based its 1995 recommendation on the existing knowledge about the prevalence and severity of soybean allergy and the level of soybean in foods. At that time, limited clinical information existed on the prevalence of soybean allergy. The Committee was influenced by a published study by Sampson and McCaskill (1985) in the United States of America showing through DBPCFC of children with atopic dermatitis that milk, eggs and peanuts were the predominant causative foods, but 5–10 percent of children in this study experienced exacerbation of their dermatitis by challenge with soy, wheat or fish. The Committee was also aware of experiences of soybean allergy occurring in milk-allergic infants who were placed on an alternative formula derived from soybean. The Committee did not have any published information on severe allergic reactions or fatalities associated with soybean. The Committee did know that soybean and soy-based ingredients were widely used in foods indicating the exposure to soybean protein would be comparatively high in global consumer diets.

The Experts Committee recommends that soybean be removed from the global list of priority allergenic foods for labelling purposes based upon (i) the generally low prevalence of soybean allergy, (ii) the lower potency of soybean proteins to trigger allergic reactions than the other protein fractions of most other priority allergenic foods and (iii) the low proportion of anaphylaxis related to soybean allergy in all regions. Due to soybean's widespread use in food products, the Committee recommend that it may be kept on a list of allergens for regional consideration.

The Expert Committee noted that many studies on the prevalence of soybean allergy were based upon self-reported data from surveys of consumers, the weakest form of evidence which was not included. The prevalence of allergy to soybean (either confirmed or probable) is higher in young infants than in school-age children; there was insufficient data to come to a firm conclusion on prevalence in adults as there was only one grade 1 study. A meta-analysis of EU studies showed that the overall prevalence of soybean allergy was 0.3 percent for food-challenge-confirmed soybean allergy (Nwaru *et al.*, 2014) and this result is almost exclusively due to a high rate among very young (< 1 year old) infants. The prevalence of soybean allergy among school-age children and adults is low with some evidence of a higher rate among school children in Japan where soybean consumption is particularly high (Ebisawa *et al.*, 2003). Infants are generally known to outgrow their soybean allergy at an early age (Savage *et al.*, 2010). The prevalence of soybean allergy may be higher among milk-allergic infants than other infants due to use of soybean-based infant as an alternative source of nutrition for milk-allergic, formula-fed infants. Among that group, the prevalence of soybean allergy appears to be as high as 14 percent with an average of 10 percent (Cordle, 2004). However, the use of soybean-based

formula as an alternative to milk formula for milk-allergic infants has become less common due to knowledge among pediatricians of the risk of the development of soybean allergy and the existence of several other alternative formulae.

The Expert Committee noted that soybean protein was less potent than the protein fractions of most other priority allergenic foods (exception: crustacean shellfish and shrimp). DBPCFC have been conducted n > 60 soybean-allergic individuals using soy flour, soy milk or soybean infant formula. Results indicated that the ED10 is in the range of 40–60 mg of soybean protein (Houben *et al.*, 2020). Thus, small amounts of soy protein exposure from cross contact due to agricultural or food manufacturing processes are less likely to pose risks to soybean-allergic consumers than other priority allergenic foods.

The Expert Committee noted that evidence indicates that the incidence of severe anaphylactic reactions to soybean among soybean-allergic individuals is rare. The Expert Committee was aware of a few published reports from 15–20 years ago of fatal reactions to soybean ingestion by soybean-allergic individuals (Yman, 2004; Yunginger *et al.*, 1991). However, the exposure doses in these few cases were quite high. The Expert Committee was influenced by the more recent publication of Baseggio Conrado *et al.* (2021) where evidence of reports of anaphylactic reactions to soybean were very rare on a global basis.

It is recommended that labelling of foods and ingredients known to cause hypersensitivities be modified as follows: Change "Peanut and soybeans and products of these" to "Peanuts and products of these".

7.3 LUPIN

Lupin can be found in a wide range of food products including bread, pastries, pies, pasta or noodles, sauces, beverages and meat such as burgers and sausages. Gluten-free or soy-free products may contain lupin. It is sometimes labelled as lupin flour, lupin flakes, lupinus, lupine, lupini or lupine beans.

Lupin is currently not a priority allergen according to the Codex, but currently requires labelling in Australia, the European Union, Morocco, New Zealand, Switzerland, Turkey, Ukraine and GSO (Gulf Cooperation Council [GCC] Standardization Organization).

The prevalence of lupin allergy has not been defined in unselected populations, for any age group or any region. Based on food-challenge studies (objective symptoms) the ED10 (including CI 95 percent) ranges between 10–100 mg proteins, and the data quantity available is considered as medium. The severity of anaphylaxis has a higher proportion in 1–2 regions; however, the number of cases of anaphylaxis reported is considered as low.

Lupin essentially poses a risk in peanut allergic individuals because primary lupin allergy seems to be rare (lack of data). Depending on studies, less than 20 percent of peanut allergic individuals would react to lupin. As for some other legumes like peas, concerns relate to the capacity of lupin to cause severe reactions in peanut allergic individuals (Shaw *et al.*, 2008; Fiocchi *et al.*, 2009; Mennini *et al.*, 2016). Should consumption patterns change (e.g. increasing use of lupin flour in pre-packaged products), lupin allergy would become a more widespread problem in countries with high prevalence of peanut allergy.

The consensus from the Expert Committee is that lupin not be listed in the global priority list but may be kept on a list of allergens for regional consideration.

7.4 BRAZIL NUT

The prevalence of Brazil nut allergy ranked overall very low, and studies relate to only two regions (Europe [the United Kingdom] and Australia). Brazil nut allergy prevalence clearly can cause severe reactions in more than three regions. The data on potency are lacking, and this data gap needs to be addressed.

The Expert Committee concluded that Brazil nut is a regional allergen which is not widely consumed across the world, and consequently, prevalence is either not studied or is low. Concerns relate to its capacity to cause severe reactions and that should consumption patterns change, it would become a more widespread problem.

The consensus from the Expert Committee is that Brazil nuts not be listed in the global priority allergen list but may be kept on a list of allergens for regional consideration.

7.5 ALMOND

Almond has been listed as a global priority allergen implicitly since the inception of the Codex List and has been included explicitly in national and regional lists (Annex II – EU Reg 1169/2011).

The evidence supporting this classification remains limited, with good quality data indicating very low prevalence of almond allergy. Data on the allergenic potency of almond are absent, an indirect indicator of a possible low number of individuals eligible for appropriate food challenges. However, severity measures, with a high proportion of anaphylaxis in three regions point to a higher global public health importance.

The Experts Committee expressed a diversity of views, reflecting their interpretation of the summary data, but also of their own expertise, drawing on studies which fell outside the criteria for inclusion, such as population questionnaires (e.g. Gupta *et al.*, 2018) or retrospective analyses of clinic patient data (e.g. Clark and Ewan, 2005). Notwithstanding this diversity, contributors unanimously concluded that almond remain a global priority allergen, with an emphasis on severity considerations. Several contributors supported a suggestion that further data should be actively generated on this allergen.

7.6 OTHER CEREALS

The Codex currently lists foods and ingredients known to cause food allergies and intolerance and whose presence should always be declared as the following: cereals containing gluten (i.e. wheat, rye, barley, oats, spelt or their hybridized strains) and their products.

Other cereals containing gluten from *Triticum* species in addition to spelt were not defined, e.g. durum wheat (semolina), emmer, einkorn, Khorasan wheat (kamut), and club wheat, or other cereals from *Hordeum* species such as farro. Also, hybridized strains of wheat were not defined but may include triticale.

Cereals in this category are associated with causing food allergies or immune-mediated reactions in sensitive individuals of two main types: IgE-mediated allergy and coeliac disease. There are also rare reports of these cereals causing reactions or problems in individuals with other food allergies (e.g. eosinophilic esophagitis), but these reports are too limited and unsubstantiated.

For the purposes of this assessment, "oats" were separated from the category "cereals containing gluten" even if regular oats are often known to be contaminated by the other cereal grains. Pure oats technically have avenin proteins and not gluten and do not have a role in toxicity for a vast majority of people with coeliac disease. Also, the scientific analysis of "cereals containing gluten" other than wheat focused mainly on rye and barley and not on spelt, hybridized, or other gluten-containing cereals; thus, these latter cereals were not considered separately.

IgE-mediated allergy has been reported to most cereals on this list. Further, there might be a potential risk of IgE-cross reactivity between gluten in cereals other than wheat and gluten in wheat. One 1995 study (Jones *et al.*, 1995) reported a potential IgE cross-reactivity rate of 20 percent between different cereals. However, this study was based on few challenges and has not been replicated. Based on the evaluations of the Expert Committee subgroups, there is very limited to no data on prevalence, severity and potency for IgE-mediated allergy to cereals other than wheat (**Table 18**). IgE-mediated allergies to these cereals are very rare, possibly in part due to their not being widely consumed. Consequently, they are not considered as a significant public health issue and would not trigger placing these cereals on the priority allergen list due to this criterion.

TABLE 18 **IGE-MEDIATED ALLERGY TO WHEAT AND OTHER CEREALS**

	POTENCY	PREVALENCE	SEVERITY
WHEAT	Medium	Low	High, 3+ regions
OTHER CEREALS	N/A	Very low	N/A

Robust prevalence study data show that coeliac disease based on robust clinical markers occurs in over 0.5 percent of individuals worldwide. In people with coeliac disease, foods that contain gluten trigger production of antibodies that attack and damage the lining

of the small intestine. Such damage limits the ability of people with coeliac disease to absorb nutrients and puts them at risk of other very serious health problems, including nutritional deficiencies, osteoporosis, slow growth, infertility, miscarriages and intestinal cancers (USFDA, 2020). Thus, foods that cause coeliac disease are important public health hazards and should be heavily considered for allergen prioritization due to significant prevalence and long-term severity within global populations.

The known HLA-DQ restricted gluten T cell epitopes, which are the drivers of coeliac disease, have recently been updated (Sollid *et al.*, 2020). Gluten-containing cereals are so named because they have toxic epitopes that can cause coeliac disease or trigger adverse reactions in sensitive individuals. While the number and types of "coeliac toxic" epitopes found in each cereal strain within this category may differ, all cereals within this category contain coeliac toxic epitopes and have a high likelihood to cause adverse health consequences for individuals with coeliac disease. However, there is a lack of clinical challenge data with other cereals containing gluten, and consequently, it is unclear how much of a role these other gluten-containing cereals play in real-world coeliac disease toxicity compared to wheat (**Table 19**).

Potentially, coeliac toxic epitopes have also been identified in oats, which might suggest that oats are also hazards to individuals with coeliac disease. However, literature supports that pure oats diets are safe for most individuals with coeliac disease. Oats only contain a subset of prolamins called avenins. These proteins contain only a very limited repertoire of coeliac motifs (Sollid *et al.*, 2020). There is evidence that the motifs present in avenins are too short and lack the multiple epitopes required to activate T cells (Shan *et al.*, 2005; Hardy *et al.*, 2015) and this evidence likely explainslikely explains the observation that oats can be safely consumed by individuals with coeliac disease (Lionetti *et al.*, 2018). Evidence is that pure oats are rarely coeliac toxic, and it may be that most adverse incidents relate to contamination of oats with other gluten-containing cereals (**Table 19**).

TABLE 19 **COELIAC DISEASE CAUSED BY WHEAT AND OTHER CEREALS**

	COELIAC TOXIC EPITOPES	CLINICAL REACTIVITY	PREVALENCE
WHEAT	Yes, strong	Yes, strong	High (> 0.5%, all regions)
OTHER GLUTEN-CONTAINING CEREALS	Yes	Yes	High (> 0.5%, all regions)
OATS (AVENINS)	Weak	Weak	N/A

Priority list consideration and discussion for "other cereals"

Wheat. Remains on global priority allergen list (discussed in earlier sections).

Cereals containing gluten. Since there is strong evidence that other gluten-containing cereals such as rye and barley have the potential to cause coeliac disease (and are potentially causes of long-term serious health consequences), they are considered to belong on the priority allergen list. There may also be a

consideration that these cereals are IgE cross reactive with wheat and thus pose a risk to wheat allergic consumers. Given these considerations, most of the Expert Committee members agreed to keep cereals in this category on the global priority allergen list.

Oats. Oats are not considered to be a priority allergenic food because they pose a low public health risk of causing IgE-mediated allergy and an absence of coeliac toxicity.

It might be considered that oats should be on a regional priority allergen list because oats are generally contaminated, and often at significant levels, with gluten containing cereals. In Canada, taking into consideration lot-to-lot variability, approximately 88 percent of commercial oats samples (n = 133) were reported to be contaminated above the Codex-recommended gluten-free level (20 ppm), gluten concentration ranging from 21 to 3 800 mg/kg of oats (Koerner *et al.*, 2011). If oats are not on a priority allergen list, the possible presence of (contaminated) oats as an ingredient remains, and several products may cause reactions in consumers with coeliac disease. For this reason, oats are included in Canadian legislation.

However, published clinical evidence clearly indicates that uncontaminated oats are safe for most individuals with coeliac disease. It is questionable whether the fact that commercial oats are often contaminated with wheat or barley should serve as a basis to have oats on a priority allergen list. Industrial processes have been developed to separate wheat and barley cereals from oats so that gluten free (< 20 ppm gluten) oats are commercially available. Also, limited production of gluten-free oats occurs from special controlled farming, harvesting and storage practices including the use of foundation seed (very pure). These gluten-free oat products may be banned from the market if oats are on a priority allergen list. Pure (or gluten free) oats are no longer part of this definition, but the Expert Committee believes there are risk management needs for gluten-contaminated commercial oats.

Given all considerations, consensus was reached by most of the Expert Committee members to not include oats on a global priority allergen list, but oats may be kept on a list of allergens for regional consideration. The Committee proposed revised definition for cereals: ***Cereals containing gluten (i.e. wheat and other Triticum species, rye and other Secale species, barley and other Hordeum species and their hybridized strains)***. The Expert Committee also recommended a footnote might be needed for the above definition: Spelt and specific cereals containing gluten other than rye and barley were not considered in this assessment, but they should also be on the priority allergen list and should be captured under the broad definition of species or hybridized strains under the genus names of *Triticum*, *Secale* and *Hordeum*. How these cereals are listed or declared on products may depend on regional laws or jurisdictions. (For example, in the United States of America, while cereals from the *Triticum* species [e.g. spelt, emmer] can be listed by their common or usual names, they also need to be listed with the common allergen source [wheat] of the Triticum genus. See Q.27 in USFDA (2006)).

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CHAPTER 8
CONCLUSIONS AND RECOMMENDATIONS

After extensive discussion on the inclusion criteria for food allergens on the global priority list, the Expert Committee reached a consensus on the importance of prevalence, potency and severity factors. All food allergens of potential concern were assessed using these criteria based on the discussion of the Expert Committee and the recommended priority food allergens are:

- Cereal containing gluten (i.e. wheat and other *Triticum* species, rye and other *Secale* species, barley and other *Hordeum* species, and their hybridized strains)
- Crustacean
- Egg
- Fish
- Peanut
- Milk
- Tree nuts (Hazelnut, cashew, walnut, pistachio, pecan, almond)
- Sesame

Food allergens included in the assessment by the Expert Committee were all those listed as part of section 4.2.1.4 of the GSLPF in addition to other food allergens included on regional or national priority lists and other emerging food allergens. The Expert Committee also assessed mustard, soybean, lupin, Brazil nut, kiwi, pine nuts, molluscan shellfish, coconut, chestnuts, celery, macadamia and buckwheat, but decided not to include them as part of the global priority list for reasons provided in this report. However, the Expert Committee also reached a consensus that some of the allergens, such as mustard, lupin, soybean, tree nuts (Brazil nut, macadamia, pine nuts), oats, celery and buckwheat may need be considered at regional levels. The risk managers could base their decision to include other food allergens on their regional priority lists on the scientific evidence, depending on their specific situation.

ANNEX 1

DETAILED AND EXTENDED DEFINITION OF IMMUNE-MEDIATED ADVERSE REACTIONS TO FOODS

COELIAC DISEASE

Coeliac disease is a chronic immune-mediated intestinal disease, which is induced in sensitive individuals by exposure to dietary gluten, including gluten proteins from wheat, rye , barley and triticale (a cross between wheat and rye). For people with coeliac disease, the prolamins found in fractions known as gliadins (from wheat), secalins (from rye) and hordeins (from barley) are considered to be the most problematic. Coeliac disease can be expressed as several subtypes and is a condition associated with typical manifestations including malabsorption syndrome, which is accompanied by weight loss and fatigue, together with gastrointestinal symptoms such as abdominal pain, vomiting, diarrhea and flatulence. The immune response results in intestinal damage along the small intestine which loses its characteristic villous architecture. Some individuals are asymptomatic but may still have mild histological lesions usually confined to the proximal small intestinal mucosa (so-called silent coeliac disease). Other asymptomatic individuals may have potential or latent coeliac disease, with only mild intestinal symptoms, and a normal villous architecture. Such individuals can have elevated intraepithelial lymphocytes (IELs), or anti-gliadin IgA and IgM and anti-endomysial serum IgA and may develop coeliac disease in the future.

Two other conditions are associated with coeliac disease:

> Dermatitis herpetiformis (DH) is diagnosed using a skin biopsy to identify the granular deposits of IgA at the tips of the dermal papillae, which are characteristic of DH. Such a diagnosis is often accompanied by the diagnostic markers associated with coeliac disease such as IgA to endomysium, and tissue transglutaminase (tTG) (Bolotin and Petronic-Rosic, 2011).

> Gluten ataxia is a condition where patients present with idiopathic sporadic ataxia wich is characterized by IgA towards tTG2 and tTG6 combined which are present in 85 percent of patients with ataxia who also have anti-gluten antibodies (Sapone *et al.*, 2012; Hadjivassiliou *et al.*, 2010)

The only current treatment for coeliac disease and its associated conditions is to avoid gluten, lifelong.

FOOD PROTEIN-INDUCED ENTEROCOLITIS SYNDROME (FPIES)

FPIES is usually caused by cow's milk and soybean but may also be triggered by other allergens such as cereal grains (rice, oats, barley) (Agyemang and Nowak-Wegrzyn, 2019). The involvement of food has been proven by food challenges with sufficient data to indicate the amount of milk required to elicit a reaction (Leonard and Nowak-Wegrzyn, 2011). It is diagnosed using a combination of clinical history, elimination diets and oral food challenge. Although infants with FPIES do not usually have food-specific IgE, those that do may be at risk of developing concurrent IgE-mediated allergies, and their FPIES may take longer to resolve. The incidence of FPIES triggered by cows' milk has been estimated to be 0.34 percent at one year old, in an Israeli birth cohort, possibly affecting males slightly more than females (Katz *et al.*, 2011). In contrast the prevalence of doctor-diagnosed FPIES in children has been estimated to be 0.51 percent (95 percent CI, 0.42–0.62) in the United States of America (Nowak-Wegrzyn *et al.*, 2019). An Australian study using a more rigorous case definition found the prevalence to be 15.4/100 000/y in infants under the age of two years but considered it was likely that the true incidence of FPIES was underreported (Mehr *et al.*, 2017).

FOOD PROTEIN-INDUCED ENTEROPATHY

Food protein-induced enteropathy is a malabsorption syndrome which is associated with a loss of villous architecture in the small intestine cause by infiltration of the mucosa by activated T cells, eosinophils and local production of IgE (Koplin *et al.*, 2014; Barni, Giovannini and Mori, 2021). It is frequently caused by cow's milk, although other foods have been implicated as triggers including soybean, egg, fish and cereals. In a Danish study, cow's milk enteropathy has been estimated to affect around two percent of infants, and it was was generally resolved by the age of one to two years, although in some instances this was in later teenage years (Høst *et al.*, 2002).

FOOD PROTEIN-INDUCED ALLERGIC PROCTOCOLITIS

Food protein-induced allergic proctocolitis manifests itself in the first three months of life with visible specks or streaks of blood mixed with mucus in the stool and affects the distal colon (Koplin *et al.*, 2014). It is not generally associated with generation of food specific IgE, and the mainstay of diagnosis is a clinical history accompanied by elimination diets and oral food challenge with the offending food.

Cow's milk and soy proteins generally act as the trigger, either as a result of passage into breast milk from maternal diet or through the use of cow's milk or soy protein infant formula. Following exclusion of the trigger food, symptoms usually resolve within 48 to 7 hours. The food then has to be excluded on an ongoing basis until tolerance is achieved (Maloney and Nowak-Wegrzyn, 2007).

EOSINOPHILIC GASTROINTESTINAL DISEASE

Eosinophilic gastrointestinal disease predominantly comprises eosinophilic oesophagitis (EoE), and (more rarely) eosinophilic gastroenteritis, and eosinophilic colitis. It is characterized by eosinophilic infiltration of the gut mucosa and may also be associated with IgE-mediated food allergy, although symptomology is dominated by the effects of eosinophilia. Based on the use of exclusion diets to diagnose and treat the condition and resolve its symptoms, there is good evidence that dietary proteins are involved in triggering EoE. Histopathology is a key aspect of diagnosing EoE with a general consensus that the condition is characterized by > 15 intraepithelial eosinophils/high-powered field (× 400) (Liacouras *et al.*, 2011; Cianferoni, 2020; Furuta *et al.*, 2007). Atopy coexists in 50–80 percent of children with EoE, and most patients improve on allergen-free diets (Furuta *et al.*, 2007). In contrast, other types of esosinophilic gastrointestinal disease do not have a clear food trigger (Cianferoni, 2020).

HEINER SYNDROME

Heiner Syndrome is a rare condition and published reports are largely related to a case series (Heiner and Sears, 1960). Despite the lack of data, it is clear the development of precipitating antibody complexes with milk proteins in the lungs is causative of the condition, which resolves when cow's milk is avoided.

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ANNEX 2
IGE-MEDIATED ALLERGIES TO BARLEY, RYE AND OATS

BARLEY AND RYE AS CROSS-REACTIVE ALLERGENS WITH WHEAT

> There is sufficient homology between barley, rye and wheat proteins to generate cross-reactive IgE responses. This is indicated by studies in individuals with Baker's asthma to flour who generate IgE responses cross-reactive *in vitro* to homologues of the α-amylase/trypsin inhibitor family from both wheat and barley which translate into *in vivo* skin test reactivity (Armentia *et al.*, 1993). Similar cross-reactivity has been observed in studies on specificity of serum IgE from Baker's asthma patients directed towards rye protein extracts, although the allergens responsible in rye were not characterized (Sander *et al.*, 2015). However, this cross-reactivity does not translated to a clinical allergy to foods containing wheat, rye and barley when it is consumed in a cooked form.

> There is similar *in vitro* evidence that the 70- and 35 k γ-secalins of rye and the γ3 hordein of barley can bind IgE, which is reactive with ω-5 gliadin from wheat – the major allergen associated with wheat-dependent, exercise-induced anaphylaxis (WDEIA) – from wheat allergic individuals. Such data indicate that rye and barley could elicit reactions in wheat allergic individuals (Palosuo *et al.*, 2001; Snégaroff *et al.*, 2013). However, there is little clinical data confirming such observations *in vivo*.

> In one study there is record of one patient with a positive oral food challenge to rye who was not IgE-reactive by skin testing, possibly because of the quality of extracts used in such diagnosis (Bengtsson *et al.*, 1996).

> Challenge-proven cases of barley allergy come from studies in young children with allergies manifesting mainly as atopic dermatitis (Eigenmann *et al.*, 1998). A recent study suggests that barley allergy is relevant in a Korean paediatric population, which includes a close relationship with wheat allergy (Lee *et al.*, 2020). Beer has been recognized as a cause of severe allergic reactions including anaphylaxis with molecules such as lipid transfer proteins involved (Figueredo *et al.*, 1999; Asero *et al.*, 2001; Quercia *et al.*, 2012).

> IgE cross-reactivity between wheat, barley and rye proteins may also extend to include oats (Varjonen *et al.*, 1994). However, a recent study of severe wheat allergy suggested that cross-reactivity with oats was weak (Srisuwatchari *et al.*, 2020). There is evidence of sensitization to oats occurring as a consequence of using topical creams based on oats (Boussault *et al.*, 2007) although this has not been confirmed in another study (Goujon *et al.*, 2009). There are few if any case reports of IgE-mediated allergies to oats due to ingestion, although traces of wheat, rye and barley may cause reactions in susceptible individuals.

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ANNEX 3
PREVALENCE EVIDENCE ASSESSMENTS

A3.1 ANIMAL FOOD ALLERGENS

A3.1.1 COW'S MILK

TABLE A1 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	Mixed	**High**

SUMMARY

> Since cow's milk allergy is most frequent in infants who progressively outgrow their allergy as they reach school age, the public health issue is greater for infants than it is for children and adults. Therefore, it was considered that the overall prevalence should be bin 4.

> Grade 1 and 2 data indicate the prevalence of challenged-confirmed cow's milk allergy is higher in infants than in school-age children or adults. This is consistent with the reports of the natural history of milk allergy where natural tolerance is developed with increasing age (low prevalence reported in school-age children in Europe and Australia and no reported prevalence of challenge-positive adults).

> There is geographic variability with prevalence notably lower in some parts of the world, such as South Africa, compared to Europe and Australia.

> All the evidence relates to milk from domestic cows (*Bos taurus*). There is no information on the prevalence of allergy to milk from other farmed animals, although homology between major allergens indicates milk from closely related species such as goats and sheep are allergenic, while allergy to milk from more distant species such as donkey and mares may be reduced (Järvinen and Chatchatee, 2009). Allergies to milk from species such as goat and sheep in isolation from allergy to cow's milk have been reported (Ah-Leung *et al.*, 2006). Thus, milk from several farmed species can represent a hazard to some individuals with cow's milk allergy.

TABLE A2 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	Low	Mixed	**High**
Children Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

TABLE A3 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
Europe, 0.6% (95% CI 0.5–0.8) for overall oral food challenge (OFC) positivity (9 studies: 3 Denmark, 2 the United Kingdom, 1 each – Iceland, Lithuania, Norway and Turkey).	> Estimates were generally higher in younger age groups than older ones and in Northern Europe than in other regions.	Nwaru *et al.*, 2014b
Infants		
Europe, 0.54% Total (Given as raw incidence) – EuroPrevall >0.62% (95% CI 0.27–1.21) – Iceland >1.26% (0.63–2.25) – the United Kingdom >1.08% (0.52–1.97) – Netherlands >0.28% (0.08–0.71) – Germany >0.6% (0.26–1.17) – Poland >0.23% (0.05–0.68) – Lithuania >0.69% (0.3–1.36) – Spain >0.3% (0.06–0.87) – Italy >0% (0–0.42) – Greece Adjusted CMA 0.74% (0.56–0.97)	> Prevalence from birth – 2 years old (pan-European DBPCFC).	Schoemaker *et al.*, 2015
South Africa, 0.1% (95% CI 0.0–0.5) – challenge positive urban >0.4% black >0.4% mixed >0.0% white 0% challenge positives rural	> Ages were: 26 months (urban), 21 months (rural). > Study population reflects ethnicity in Cape Town. > Allergy rates in the rural population were too low to calculate prevalence of food allergy.	Botha *et al.*, 2019
Australia, 1.5% (95% CI 1.1–2.1)	> Prevalence at age 1 year old in Melbourne	Peters *et al.*, 2017
School-age children		
Australia, 0.2% confirmed by food challenge	> Aged 10–14 years, Melbourne	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A3 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
1.6% (95% CI 1.2–1.9) for OFC or history of cow's milk allergy	> Estimates were generally higher in younger age groups than in older ones and in Northern Europe than in other regions.	Nwaru *et al.*, 2014b
Infants (Change age categories as appropriate if needed)		
No data		
School-age children		
Europe Probable food allergy (95% CI) >1.70% (0.68–3.24) – Lodz >0.89% (0.12–2.46) – Madrid >0.89% (0.01–3.17) – Vilnius >1.16% (0.34–2.52) – Utrecht >0.00% (0.00–0.49) – Zurich >0.56% (0.00–2.51) – Athens >0.37% (0.02–1.23) – Reykjavik	> Prevalence in school-age children mean age ~9 years old pan-European	Lyons *et al.*, 2020
China, India and Russian Federation Probably food allergy (95% CI) >0.00% (0.00–0.06) – China, Hong Kong SAR >0.00% (0.00–0.07) – Guangzhou >0.04% (0.01–0.015) – Shaoguan >0.00% (0.00–0.07) – India >0.05% (0.02–0.11) – Tomsk	> Prevalence in school-age children mean age ~8–10 years old	Li *et al.*, 2020
Adults		
Europe Probable food allergy (95% CI) >0.12% (0.01–0.74) – Lodz >0.18% (0.00–0.97) – Madrid >0.00% (0.00–0.21) – Utrecht >0.24% (0.00–1.02) – Zurich >0.00% (0.00–0.68) – Athens >0.00% (0.00–0.28) – Reykjavik	> Prevalence in adults median age ~36 years	Lyons *et al.*, 2019

A3.1.2 HEN'S EGG

TABLE A4 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE	Insufficient data to determine low or high	Very low	Low	Mixed	**High**

SUMMARY

> The data found in the literature for grade 1 prevalence demonstrate that (hen's) egg allergy exceeds one percent in three regions of the world (Europe, South Africa and Australia) and fulfils the criteria for bin 4.

> Similar to cow's milk, hen's egg allergy is most frequent in infants who progressively outgrow their allergy as they reach school age; the public health issue is greater for infants than children or adults.

> Prevalence is high in infants in northern European countries and is very low in some countries and environments, e.g. Athens, Greece (infants); Zurich, Switzerland (school-age children); Utrecht, Netherlands (adults).

> The meta-analysis in 2014 indicates rates of 0.2–1.0 percent for food challenge or history confirmed food allergy. The upper bound is significantly lower than the challenge proven rates in infants which appear to be between ~2–9 percent.

> All the evidence relates to eggs from domestic hens (*Gallus gallus domesticus*). There are reports indicating allergy to hen's egg results in IgE responses reactive to egg allergens from other species such as duck (Langeland, 1983) with the allergenicity of eggs from ancient species (Araucana and Maran) being similar to that of domesticated hens (Egger *et al.*, 2011). However, allergies to eggs from other farmed birds such as duck and goose (Añíbarro *et al.*, 2000) and quail (Caro Contreras *et al.*, 2008) independent of allergies to hen's egg have been reported.

TABLE A5 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	Low	Mixed	**High**
Children Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	**Mixed**	High
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

TABLE A6 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
0.2% (95% CI 0.2–0.3) for OFC positivity	> Estimates were generally higher in younger age groups than older ones and in Northern Europe than in other regions.	Nwaru *et al.*, 2014b
Infants		
Europe > 0.84% (95% CI 0.67–1.03) – down to 0.0% (95% CI 0.0–0.42); given as raw incidence > 2.18% (95% CI 1.27–3.47) in the United Kingdom and down to 0.07% (95% CI 0.00–0.63)	> Prevalence from birth to 2 years old > pan-European	Xepapadaki *et al.*, 2016
South Africa 1.8% (95% CI 1.1–2.7) Urban > 3.6% black > 3.1% mixed > 5.3% white 0% Rural	> Ages were 26 months (urban), 21 months (rural). > Study population reflects ethnicity in Cape Town. > Allergy rates in the rural population were too low to calculate prevalence of food allergy.	Botha *et al.*, 2019
Australia 9.5% (96% CI 8.7–10.3)	> Prevalence at age 1 year old in Melbourne	Peters *et al.*, 2017
Australia 1.2%	> Prevalence at age 4 years old in Melbourne	Peters *et al.*, 2017
School-age children		
Europe 0.05%	> Prevalence at mean age 8.3 years old	Grabenhenrich *et al.*, 2020
Australia 0.5%	> Age 14 years, Melbourne	Sasaki *et al.*, 2018

TABLE A6 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
1.0% (95% CI 0.8–1.3) for OFC or history of egg allergy	Estimates were generally higher in: >younger age groups than older ones and >Northern Europe than in other regions.	Nwaru *et al.*, 2014b
School-age children		
China, India and Russian Federation 0.2 (China, Hong Kong SAR) 0.04 (Guanzhou) 0.00 (Shaoguan) 0.05 (India) 0.01 (Tomsk)	>Prevalence in children aged 8.6–10.4 in China (China, Hong Kong SAR, Guanzhou, Shaoguan), India (Bangalore, Mysore) and Russian Federation (Tomsk)	Li *et al.*, 2020
Europe 0.89% (95% CI 0.14–2.46) Madrid 0.85% (95% CI 0.1–3.06) Athens 0.74% (95% CI 0.15–1.84) Reykjavik 0.76% (95% CI 0.16–1.69) Lodz 0.44% (95% CI 0.02–2.28) Vilnius 0.21% (95% CI 0.00–0.49) Utrecht 0.00% (95% CI 0.00–0.49) Zurich		Lyons *et al.*, 2020
Adults		
Europe 0.31% (95% CI 0.01–1.11) in Lodz (Poland) 0.00% (95% CI 0.00–0.21) in Utrecht (Netherlands)	>Prevalence in adults median age ~36 years	Lyons *et al.*, 2019

A3.1.3 FISH

TABLE A7 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

SUMMARY

> Prevalence of fish allergy is higher in adults than in school-age children, which appears to be higher than those reported in infants.

> Prevalence is high in children in Spain (grade 2) and is very low in some regions.

> Most data are from cod; the major allergen is parvalbumin, which is found in many fish species although at much lower levels in species with dark muscle, such as tuna (Kuehn *et al.*, 2014). A challenge study in fish allergic subjects suggested that in general, more patients were allergic to codfish compared to other fish species such as salmon and mackerel, although monosensitization to other species, such as salmon, is observed (Sørensen *et al.*, 2017). Therefore, cod has been used in the prevalence studies to represent fish allergy.

TABLE A8 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

TABLE A9 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
0.1% (95% CI 0.02–0.2) for food-challenge positivity	> Life-time prevalence calculated for all ages.	Nwaru *et al.*, 2014b
Infants		
the United Kingdom 0.1% (95% CI 0.00, 0.60)	> Age 0–1 year	Venter *et al.*, 2008
0.0%	> Age 2 and 3 years	Venter *et al.*, 2008
Children		
Europe 0% (95% CI 0–0.1%) – 0.3% (95% CI 0–2%) (Europe, highest in Iceland and Denmark; lowest in Turkey and the United Kingdom) Thailand 0.3% (2 OFC positive to fish/656)	Systematic review >Europe (4 studies) >Thailand (1 study)	Moonesinghe *et al.*, 2016; Santadusit *et al.*, 2005
Australia 0.2% (8/5016)		Sasaki *et al.*, 2018
Europe 0.1%	> 0.05% each for white or oily fish	Grabenhenrich *et al.*, 2020
Adults		
Systematic review >Europe (3 studies)	> < 0.3% [95% CI 0–~1%]	Moonesinghe *et al.*, 2016
Systematic review & meta-analysis >Europe (3 studies)	> 0.15% [95%CI 0–0.4]	Nwaru *et al.*, 2014b

TABLE A9 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
0% [95%CI 0–0.1]	Systematic review & meta-analysis >Europe (2 studies) Point prevalence in infants for combination of OFC and allergy diagnosed by history	Nwaru *et al.*, 2014b
Infants		
Systematic review >Thailand (1 study)	>0.1% (0–1.3)	Moonesinghe *et al.*, 2016
Children		
Europe: >Poland (Lodz) >Spain (Madrid) >Lithuania (Vilnius) >Netherlands (Utrecht) >Switzerland (Zurich) >Greece (Athens) >Iceland (Reykjavik)	>(0.00–0.37) >0.53 (0.02–1.85) >(0.00–0.86) >0.11 (0.02–0.74) >0.14 (0.04–0.98) >0.28 (0.07–1.89) >0.15 (0.01–0.80)	Lyons *et al.*, 2020
China (8.5–9.1y) (Probable food allergy as defined by reported symptoms and positive SPT/IgE 0.7 kU/L)	>As fish (species unidentified) >0.20 (0.11–0.34) China, Hong Kong SAR >(0.00–0.07) Guangzhou >0.00 (0.00–0.07) Shaoguan	Li *et al.*, 2020
Russian Federation (8.9 ± 1.1 y) (Probable food allergy as defined by reported symptoms and positive SPT/IgE 0.7 kU/L)	>As fish (species unidentified) >0.34 (0.25–0.45)	Li *et al.*, 2020
China Epi study (3–6 y) n=4 151	>0.2% (9/4151)	Dai *et al.*, 2020
Adults		
Europe: >Switzerland (Zurich) >Spain (Madrid) >Iceland (Reykjavik) >Poland (Lodz) >Netherlands (Utrecht) >Greece (Athens)	>(0.00–0.33) >0.38 (0.01–1.51) >0.25 (0.00–0.98) >(0.00–0.44) >0.20 (0.00–0.86) >0.00 (0.00–1.84)	Lyons *et al.*, 2019

A3.1.4 CRUSTACEAN SHELLFISH

TABLE A10 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	**Mixed**	High

SUMMARY

> The combination of grade 1 and grade 2 data for adults and children indicated that overall the prevalence fell within bin 3.

> The data mainly related to shrimp, with data on crab coming from China and Thailand.

> There is evidence that crustacean food allergy is more prevalent in Southeast Asia (such as Thailand), Australia and parts of Europe, such as Spain, where crustacean seafood are more widely consumed.

> Prevalence of crustacean shellfish allergy is higher in children and adults than in infants.

> Some people may react to certain species of crustacea (both interspecies and intercrustacean variations).

> The major allergen is tropomyosin which, along with other allergens such as myosin light chain and arginine kinase, shows high levels of homology between crustacean shellfish species and is responsible for cross-reactive allergies (Lopata *et al.*, 2010). Such homology also results in cross-reaction with inhalant allergens from dust mite (Lopata *et al.*, 2010) and has been linked to reactions to insects used for food (van Broekhoven *et al.*, 2016) which can cause reactions in shrimp allergic subjects (Broekman *et al.*, 2016).

TABLE A11 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	Mixed	High
Adults	Insufficient data to determine low or high	Very low	Low	Mixed	High

TABLE A12 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
0.1% (95% CI 0.06–0.3) for OFC positivity	> All ages	Nwaru *et al.*, 2014a
0.1% (CI 0–0.3)	> Infants: Europe (2 studies – Denmark, the United Kingdom)	Nwaru *et al.*, 2014a
Infants		
< 0.1% (95%CI 0–4.2%)	> Denmark	Osterballe *et al.*, 2005
Children		
< 0.1% (95% 0–~1%)	> Denmark	Osterballe *et al.*, 2005
0.3% (CI 0.1–1.2) 1.11% (CI 0.41–2.98)	> Thailand (2 studies) > Shrimp	Santadusit *et al.*, 2005; Lao-araya and Trakultivakorn, 2012
0.2% (CI 0–1.4)	> Thailand > Crab (1 patient only, also cross-reactive to shrimp)	Lao-araya and Trakultivakorn, 2012
0.3% (13/5016)	> Australia; reported as Shellfish	Sasaki *et al.*, 2018
0.1%	> iFAAM-EuroPrevall cohort at school-age follow up	Grabenhenrich *et al.*, 2020
Adults		
~0.3% (CI 0.1–1.0)	> Denmark	Osterballe *et al.* 2005

TABLE A12 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
No data		
Infants		
No data		
Children		
> (0.00–0.37) > 0.71 (0.06–2.16) > (0.00–0.86) > (0.00–0.37) > 0.14 (0.04–0.98) > (0.00–0.88) > 0.30 (0.01–1.10)	Europe: > Poland (Lodz) > Spain (Madrid) > Lithuania (Vilnius) > Netherlands (Utrecht) > Switzerland (Zurich) > Greece (Athens) > Iceland (Reykjavik)	Lyons *et al.*, 2020
0.1%	> Canada	Ben-Shoshan *et al.*, 2010
0.1% (shrimp, 5/4 151) 0.1% (crab, 4/4 151)	> China (Wenzhou) > Epi study (3–6 y) n = 4 151	Dai *et al.*, 2020
Shrimp 1.05% (0.82–1.33) China, Hong Kong SAR 0.18% (0.10–0.33) Guangzhou 0.65% (0.46–0.90) Shaoguan Crab 0.20% (0.11–0.34) China, Hong Kong SAR 0.07% (0.03–0.18) Guangzhou 0.43% (0.28–0.65) Shaoguan	> China	Li *et al.*, 2020
0.02% (0.00–0.06)	> Shrimp > Russian Federation (8.9 ± 1.1 y) (n = 12 997)	Li *et al.*, 2020
0.00% (0.00–0.07)	> Shrimp > India (9.1 ± 1.8 y) (n = 5 677)	Li *et al.*, 2020
Adults		
~0.2% (CI 0.1–1.0)	> Denmark	Osterballe *et al.*, 2009
0.42 (0.04–1.29) 1.47 (0.43–3.27) 0.57 (0.09–1.54) 0.35 (0.01–1.33) 0.44 (0.04–1.30) 0.00 (0.00–1.84)	Europe: > Switzerland (Zurich) > Spain (Madrid) > Iceland (Reykjavik) > Poland (Lodz) > Netherlands (Utrecht) > Greece (Athens)	Lyons *et al.*, 2019
0.7%	Canada	Ben-Shoshan *et al.*, 2010

A3.1.5 MOLLUSCAN SHELLFISH

TABLE A13 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

SUMMARY

> No grade 1 evidence is available for prevalence of molluscan shellfish allergy as no prevalence studies using food challenges to confirm allergy to molluscs are available.

> Grade 2 evidence was reported for one adult in Denmark giving a prevalence of 0.1 percent to octopus (Osterballe *et al.*, 2009).

> This was also observed by EFSA in the 2014 opinion, which also commented on the difficulty of establishing the prevalence of IgE-mediated adverse reactions because of reactions mediated by shellfish toxins as well as the issues of IgE cross-reactivity between individuals sensitized to dust mite and crustacean shellfish (EFSA Panel on Dietetic Products and Allergies, 2014).

TABLE A14 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

A3.2 PLANT FOOD ALLERGENS

A3.2.1 CEREALS CONTAINING GLUTEN

A3.2.1.1 Wheat and species thereof

TABLE A15 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	**Mixed**	High
IgE-mediated food allergy					
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

SUMMARY

> Cereals grains from the *Triticeae* established to be toxic for individuals with coeliac disease are wheat, rye and barley by virtue of their sharing coeliac toxic motifs (Sollid *et al.*, 2020). These epitopes can be found in the seed storage prolamins of oats although at a lower density than in prolamins from other cereals (avenins) (Daly *et al.*, 2020), but evidence from clinical studies suggest that oats can be safely consumed by the vast majority of individuals with coeliac disease (Lionetti *et al.*, 2018). In addition, oats are often contaminated by other cereals containing gluten such as wheat or rye, explaining why some jurisdictions considered oats as a potential gluten source.

> Omega-5-gliadin from wheat is recognized to be one of the major causes of food-dependent exercise-induced anaphylaxis (FDEIA). This allergen is not found in other species of the *Triticeae*, which may explain why it is confined to *T. aestivum* and related species (*T. Durum*, *Speltiodes* etc.) (Daly *et al.*, 2020).

> Many good quality prevalence studies that met grade 1–2 evidence have been conducted over the past ten years for wheat allergy and coeliac disease.

> Data regarding the natural history of wheat allergy suggest that wheat allergy is more common in children, and up to 65 percent may outgrow it by adulthood (Keet *et al.*, 2009).

> A condition known as non-coeliac gluten sensitivities (NCGS) has been described in a small number of patients and is a matter of debate in the field with a considerable overlap with irritable bowel syndrome and some subjects possibly having undiagnosed coeliac disease (Potter *et al.*, 2018). While this hypersensitivity has been demonstrated by DBPCFC, there is no known immune-mediated mechanism. Thus, since the current prioritization includes only immune-mediated food allergies, prevalence data on NCGS were not considered.

> Other food disease entities associated with cereal allergies include eosinophilic gastroenteropathies, food protein-induced enterocolitis syndrome (oats and barley) and food protein induced enteropathy (wheat), not considered in this assessment.

> The evidence that rye, barley and oats cause IgE-mediated allergies is weak.

TABLE A16 **AGE GROUP SUMMARY FEEDING INTO DECISION REGARDING IGE-MEDIATED FOOD ALLERGY**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

Epidemiology of IgE-mediated allergy to wheat

> Most cereal IgE-mediated allergy prevalence data is from North America and Europe, but there are representative studies in unselected populations from all parts of the world.

> There is evidence of a number of systematic reviews including a review of European prevalence data (Zuidmeer *et al.*, 2008) and a meta-analysis of food allergies by Nwaru *et al.* (2014b) which have looked at wheat allergy prevalence.

> There are reported positive wheat challenge tests in children with a prevalence between 0.2 percent (9–12 years old) and 0.5 percent (0–14 years old) (grade 1) (Zuidmeer *et al.*, 2008)

> Based on the meta-analysis for wheat allergy (Nwaru *et al.*, 2014b), relevant findings include:

  » 0.1 percent for food-challenge positivity (grade 1)

  » 0.3 percent for food challenge or history (grade 2)

TABLE A17 **EVIDENCE**

GRADE 1 BASED ON ANTI-TISSUE TRANSGLUTAMINASE (IgA-tTG) IgA and/or anti-endomysial IgA (IgA-EMA) AND intestinal biopsy as a confirmation of coeliac disease	RESULTS/COMMENTS	REFERENCE
Meta-analysis (IC95%)		
0.7% (0.4–0.8%)	> Coeliac disease confirmed by biopsy > (meta-analysis; global > 4 regions; n ≈ 138 000)	Singh *et al.*, 2018
0.8% (0.6–1.1%)	> Europe	
0.6% (0.4–0.8%)	> Asia	
0.4% (0.1–0.6%)	> South America	
0.5%	> North America	
0.5% (0.2–0.9%)	> Africa	
0.8% (0.2–1.7%)	> Oceania	
Children (IC95%)		
0.9% (0.6–1.3%)	> Coeliac disease confirmed by biopsy > (meta-analysis; global > 4 regions; n ≈ 66 000)	Singh *et al.*, 2018
Adults (IC95%)		
0.5% (0.3–0.8%)	> Coeliac disease confirmed by biopsy > (meta-analysis; global > 4 regions; n ≈ 40 000)	Singh *et al.*, 2018
TOTAL Adults and children		
0.58% (0.53–0.69%)	> Prevalence (Caucasian individuals)	Biagi *et al.*, 2010
Adults (IC95%)		
0.35% (0.11%-0.59%)	> Prevalence (in Northwest China; n = 2 278)	Zhou *et al.*, 2020

TABLE A17 **EVIDENCE** (continued)

GRADE 2 BASED ON ANTI-TISSUE TRANSGLUTAMINASE (IGA-TTG) IGA AND/OR ANTI-ENDOMYSIAL IGA (IGA-EMA)	RESULTS/COMMENTS	REFERENCE
Meta-analysis (IC95%)		
1.4% (1.1–1.8%)	> Coeliac disease seroprevalence > (meta-analysis; global > 4 regions; n ≈ 138 000)	Singh *et al.*, 2018
1.3% (1.1–1.5%)	> Europe	
1.8% (1–2.9%)	> Asia	
1.3% (0.5–2.5%)	> South America	
1.4% (0.7–2.2%)	> North America	
1.1% (0.4–2.2%)	> Africa	
1.4% (1.1%–1.8%)	> Oceania	
TOTAL Adults and children (IC95%)		
0.69% (0.64–0.74%)	> Coeliac disease Seroprevalence (Caucasian individuals)	Biagi *et al.*, 2010
Adults (IC95%)		
0.36% (0.28–0.46)	> Coeliac disease Seroprevalence (Chinese individuals; n = 19 778)	Yuan *et al.*,2017

TABLE A17 **EVIDENCE** (continued)

WHEAT IGE-MEDIATED ALLERGY		
GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
0.1% (0.01–0.2%)	> Europe; point prevalence	Nwaru *et al.*, 2014b
Infants		
0%	> Denmark (3 years old)	Osterballe *et al.*, 2005
School-age children		
0.2%	> the United Kingdom (9–12 years old)	Venter *et al.*, 2006
0.3%	> the United Kingdom (6 years old)	Venter *et al.*, 2006
0.05	> OFC confirmed food allergy (2 of 4 291 subjects aged 4)	Peters *et al.*, 2017
0.5%	> Germany (0–14y)	Roehr *et al.*, 2004
Adults		
No data		

TABLE A17 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
0.3% (0.02–0.6%)	> Europe (based on OFC positivity or clinical history)	Nwaru *et al.*, 2014b
Infants (IC95%)		
0.2% (overall prevalence: 5%)	> the United Kingdom (EuroPrevall birth cohort, n = 1 140)	Grimshaw *et al.*, 2015
Children (age 7–10) (IC95%)		
0.14% (0.04–0.98%)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2020
0.15% (0.01-0.80)	> Iceland (EuroPrevall)	
0% (0–0.56%)	> Spain (EuroPrevall)	
0% (0–0.37%)	> Poland (EuroPrevall	
0.21% (0–0.97%)	> Netherlands (EuroPrevall)	
0% (0–0.88%)	> Greece (EuroPrevall)	
0% (0–0.86%)	> Lithuania (EuroPrevall)	
Adults (> age 18) (IC95%)		
0.19% (0–0.73%)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2019
0.1% (0–0.6%)	> Iceland (EuroPrevall)	
0.37% (0.02–1.31%)	> Spain (EuroPrevall)	
0% (0–0.36%)	> Poland (EuroPrevall)	
0.05% (0.01–0.36%)	> Netherlands (EuroPrevall)	
0% (0–0.68%)	> Greece (EuroPrevall)	
0.02% (0.87)	> Russian Federation (EuroPrevall-INCO)	
0.02% (0.87)	> Russian Federation (EuroPrevall-INCO)	Li *et al.*, 2020
0% (0–0.07%)	> China (EuroPrevall-INCO)	
0% (0–0.06%)	> China, Hong Kong SAR (EuroPrevall- INCO)	
0% (0–0.06%)	> India (EuroPrevall-INCO)	Li *et al.*, 2020
0.02%	> India	Mahesh *et al.*, 2016
0% (0–0.07%)	> Russian Federation (EuroPrevall-INCO)	Li *et al.*, 2020

A3.2.1.2 Barley

TABLE A18 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

SUMMARY

> There are no systematic reviews looking specifically at barley allergy.

> Except for rye being an immune-mediated trigger for coeliac disease and some other gluten-related disorders, there is little evidence that barley is a significant allergen causing IgE-mediated reactions.

> More studies are needed to document the ability of barley to trigger IgE-mediated adverse reactions to food.

A3.2.1.3 Rye

TABLE A19 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

SUMMARY

> There are no systematic reviews looking specifically at rye allergy.

> Except for rye being an immune-mediated trigger for coeliac disease and some other gluten-related disorders, there is little evidence that rye is a significant allergen causing IgE-mediated reactions (see **Annex 2** for more information).

> More studies are needed.

A3.2.1.4 Oats

TABLE A20 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

SUMMARY

> There are no systematic reviews looking specifically at oat allergy.

> Pure oat is not recognized to trigger symptoms in people with coeliac disease and other gluten-related disorders, but oat is often contaminated by other cereals containing gluten such as wheat or rye. More information is provided in **Annex 2**.

> More studies are needed to document the ability of oats to trigger IgE-mediated adverse reactions to food.

A3.2.2 FRUIT AND VEGETABLES

A3.2.2.1 Celery

TABLE A21 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> The regional specificity of the allergy means it was classified as very low.

> Allergy to celery is highly localized, even in the region where it is reported (Europe) and is strongly associated with pollen sensitization and oral allergy syndrome.

> Consensus was that this was a geographically limited allergy with a higher prevalence of probable food allergy in Poland and Switzerland, with two out of six EuroPrevall centres yielding prevalence of 0 percent.

> Prevalence of allergy was only confirmed in one out of two adults eligible for DBPCFC in the EuroPrevall cross-sectional population study.

> Celery allergy is largely a condition found in older children and adults.

TABLE A22 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

TABLE A23 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
No data		
Infants (Change age categories as appropriate if needed)		
No data		
School-age children		
No data		
Adults		
1 positive DBPCFC (Zurich) out of 2 eligible participants challenged (50%) This gives a prevalence of 0.2% in Switzerland.	> EuroPrevall	Lyons *et al.*, 2019

TABLE A23 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants (Change age categories as appropriate if needed)		
None		
School-age children		
0.14 (0.04–0.98)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2020
0.00 (0.00–0.35)	> Iceland (EuroPrevall)	
0.00 (0.00–0.56)	> Spain (EuroPrevall)	
1.24 (0.40–2.60)	> Poland (EuroPrevall	
0.00 (0.00–0.37)	> Netherlands (EuroPrevall)	
0.00 (0.00–0.88)	> Greece (EuroPrevall)	
0.00 (0.00–0.86)	> Lithuania (EuroPrevall)	
Adults		
0.24 (0.01–0.81)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2019
0.33 (0.03–1.03)	> Iceland (EuroPrevall)	
0.00 (0.00–0.44)	> Spain (EuroPrevall)	
0.07 (0.02–0.63)	> Poland (EuroPrevall)	
0.03 (0.03–0.32)	> Netherlands (EuroPrevall)	
0.00 (0.00–0.68)	> Greece (EuroPrevall)	

A3.2.2.2 Kiwi

TABLE A24 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

SUMMARY

The prevalence of kiwi allergy was classified in bin 2 since grade 1 data indicated it was very low for school-age children (with no data available for infants of adults). Grade 2 indicated the prevalence was low in school-age children and adults in one region (Europe).

TABLE A25 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

TABLE A26 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
1%–1.4% (infants and school-age children) 0.1% (adults)	> Systematic search of population-based studies (1990–2008) (fruits, vegetables/ legumes, tree nuts, wheat, soy, cereals, and seeds). > 36 studies included, with data from a total of over 250 000 children and adults. > Only 6 studies included food-challenge tests.	Zuidmeer *et al.*, 2008
Infants (Change age categories as appropriate if needed)		
No data		
School-age children		
0.1% (7/5 016)	> Aged 14 years, Melbourne, Australia	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A26 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants (Change age categories as appropriate if needed)		
No data		
School-age children		
0.4% overall prevalence **Lodz** 0.31 (0.01–1.14) **Madrid** 1.06 (0.19–2.74) **Vilnius** 0.44 (0.02–2.28) **Utrecht** 0.63 (0.09–1.72) **Zurich** 0.27 (0.00–1.29) **Athens** 0.00 (0.00–0.88) **Reykjavik** 0.15 (0.01–0.80)	> Prevalence in school-age children mean age ~9 years old > pan-European study	Lyons *et al.*, 2020
Adults		
0.5% overall prevalence **Zurich** 1.34 (0.60–2.42) **Madrid** 0.64 (0.11–1.77) **Reykjavik** 0.31 (0.02–0.99) **Lodz** 0.30 (0.01–1.09) **Utrecht** 0.57 (0.15–1.29) **Athens** 0.00 (0.00–0.68)	> Prevalence (Probable FA) in adults median age ~36 years	Lyons *et al.*, 2019

A3.2.3 LEGUMES

A3.2.3.1 Lupin

TABLE A27 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

SUMMARY

> The prevalence of lupin allergy has not been defined in unselected populations, for any age group or any region.

> Lupin may pose a risk to peanut allergic individuals due to cross-reactivity, although there are potential issues over reports relying simply on IgE cross-reactivity without demonstration of clinical reactivity to lupin (Ballabio *et al.*, 2013; 2010; Bähr *et al.*, 2014; Peeters *et al.*, 2007; Gayraud *et al.*, 2009).

> Data on lupin sensitization are available and vary widely (Gayraud *et al.*, 2009; Peeters *et al.*, 2007).

> Clinical relevance of primary lupin allergy seems to be rare, but cases of allergic reactions to lupin without peanut allergy/sensitization have been reported.

TABLE A28 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

A3.2.3.2 Peanut

TABLE A29 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	Mixed	**High**

SUMMARY

> Prevalence of challenge confirmed food allergy is generally < probable < self-reported IgE-mediated food allergy.

> Prevalence of peanut allergy, however defined, is higher in children and young adults than infants and older adults.

> Prevalence is high in Western European countries and is higher in countries such as the United Kingdom, Canada, Australia and the United States of America and is very low in inland China and rural South Africa.

> The meta-analysis in 2014 indicates rates of 0.2–1.6 percent for a food-challenged or history-confirmed food allergy. The upper bound is significantly lower than the rates of challenge-proven peanut allergy in infants in Australia, which is 3.1 percent.

TABLE A30 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	Low	Mixed	**High**
Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	Mixed	**High**
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

TABLE A31 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
0.2% (95% CI for 0.2–0.3) for OFC positivity	> Estimates were higher in older children compared to infants and higher in Western Europe than other regions.	Nwaru *et al.*, 2014b
Infants		
0.7% (95% CI 0.3–1.3) Urban >1.5% black >1.5% mixed >0% white Rural 0%	Ages were >26 months (urban) >21 months (rural) >Study population reflects ethnicity in Cape Town. >Allergy rates in the rural population were too low to calculate prevalence of food allergy.	Botha *et al.*, 2019
3.1% (95% CI 2.7–3.6)	> Prevalence at age 1 year old in Melbourne	Peters *et al.*, 2017
School-age children		
0.14%	> Prevalence at mean age 8.3 years	Grabenhenrich *et al.*, 2020
0.57% (based on 21.3% challenge positive subjects with probable food allergy)	> Aged 14 years, Melbourne, Australia	Sasaki *et al.*, 2018
1.03 (0.67–1.39)	> Canada	Ben-Shoshan *et al.*, 2010
Adults		
0.26 (0.18–0.34)	> Canada	Ben-Shoshan *et al.*, 2010

TABLE A31 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
> 1.6% (95% CI 1.2–1.9) for OFC or history of peanut allergy	> Estimates were higher in older children compared to infants and higher in Western Europe than other regions.	Nwaru *et al.*, 2014b
Infants (Change age categories)		
No data		
School-age children		
0.89 (0.12–2.46) (Madrid) 0.00 (0.00–0.86) (Vilnius)	> Prevalence in school-age children mean age ~9 years old > PanEuropean	Lyons *et al.*, 2020
0.10 (0.05–0.21) (China, Hong Kong SAR) 0.00 (0.00–0.07) (Guangzhou)	> Prevalence in school-age children mean age ~8–10 years old > China, India and Russian Federation	Li *et al.*, 2020
2.8%	> Prevalence at mean age 8.3 years	Grabenhenrich *et al.*, 2020
2.7% (95%CI, 2.3–3.2)	> Aged 14 years, Melbourne, Australia	Sasaki *et al.*, 2018
Adults		
0.45 (0.05–1.45) (Madrid) 0.00 (0.00–0.28) (Reykjavik)	> Prevalence in adults median age ~36 years	Lyons *et al.*, 2019

A3.2.3.3 Soybean

TABLE A32 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

SUMMARY

> Overall prevalence for soybean allergy is low in all age groups although there is variation across the world. Consequently, it has been assigned to bin 2 (low).

> The meta-analysis in 2014 indicates rate of 0.3 percent for food-challenge-confirmed food allergy, but that is almost exclusively due to a high rate in very young (< 1-year-old) infants.

TABLE A33 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

TABLE A34 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
0.26% overall; all but one case in infants < 1 year old 0.3% (95% CI 0.1–0.4)	> Includes 5 studies (3 Denmark; 1 Germany; 1 Iceland)	Nwaru *et al.*, 2014b
Infants (Change age categories as appropriate if needed)		
0.07%	> Iceland study site part of the EuroPrevall birth cohort	Kristinsdóttir *et al.*, 2011
0%	> Iceland (history and SPT)	Kristjansson *et al.*, 1999
0%	> Sweden (history and SPT)	Kristjansson *et al.*, 1999
0.4% (0.0–0.8)	> the United Kingdom EuroPrevall birth cohort	Grimshaw *et al.*, 2015
0% Urban 0.4% (0.1–0.8) Rural 0.0%	> Ages were 26 months (urban) and 21 months (rural). > Study population reflects ethnicity in Cape Town. > Allergy rates in the rural population were too low to calculate prevalence of food allergy.	Botha, *et al.*, 2019
One positive challenge to soybean reported in a cohort of 4 291 children (0.02%).	> No other data reported. Prevalence at age 1 years old in Melbourne.	Peters *et al.*, 2017
School-age children		
0% (0/712)	> Denmark (part of Nwaru)	Osterballe *et al.*, 2005
0.54% (4.739)	> Germany (part of Nwaru)	Roehr *et al.*, 2004
0.02% (1/5 016)	> Australia	Sasaki *et al.*, 2018
0.3% (62/18 880)	> the United Kingdom (both adults and children)	Young *et al.*, 1994
Adults		
0 (0/936)	> Denmark (part of Nwaru)	Osterballe *et al.*, 2005
0.1% (0.0%–0.8%)	> Denmark (part of Nwaru)	Osterballe *et al.*, 2009

TABLE A34 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants (Change age categories as appropriate if needed)		
No data		
School-age children		
0.00 (0.00–0.49)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2020
0.21 (0.00–0.97)	> Netherlands (EuroPrevall)	
0.31 (0.01–1.14)	> Poland (EuroPrevall)	
0.00 (0.00–0.86)	> Lithuania (EuroPrevall)	
0.07 (0.03–0.63)	> Iceland (EuroPrevall)	
0.18 (0.02–1.15)	> Spain	
0.00 (0.00–0.88)	> Greece	
0%	> South Africa	Botha *et al.*, 2019
0.03%	> Israel	Dalal *et al.*, 2002
Adults		
0.08 (0.02–0.56)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2019
0.03 (0.03–0.32)	> Netherlands (EuroPrevall)	
0.00 (0.00–0.36)	> Poland (EuroPrevall)	
0.00 (0.00–0.28)	> Iceland (EuroPrevall)	
0.00 (0.00–0.44)	> Spain	
0.00 (0.00–0.68)	> Greece	

A3.2.4 SEEDS

A3.2.4.1 Buckwheat

TABLE A35 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low < 0.5% in all regions	Mixed > 1% in one region and 0.5–1% in at least one other region	High > 1 in at least 2 regions

SUMMARY

> Grade 1 data were lacking, and consequently, the assessment was made solely based on grade 2 data which was only available for school-age children and adults.

> Prevalence of buckwheat allergy is very low in school-age children and appears to be ~0 percent in adults in the centres studied.

TABLE A36 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	Insufficient data to determine low or high	**Very low**	**Low**	Mixed	High

No grade 1 data were identified.

TABLE A37 **EVIDENCE**

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
No data		
Infants		
No data		
School-age children		
0.05% (2/3 907 ages 6–7 years old) 0% (0/3 975 ages 12–13 years old)	> Republic of Korea	Ahn *et al.*, 2012
0.14% (0.04–0.98)	> Switzerland (probable food allergy) – EuroPrevall	Lyons *et al.*, 2020
0% (0.00–0.37)	> Netherlands (probable FA) – EuroPrevall	
0% (0.00–0.37)	> Poland (probable FA) – EuroPrevall	
0% (0.00–0.86)	> Lithuania (probable FA) – EuroPrevall	
0.07% (0.03–0.63)	> Iceland (probable FA) – EuroPrevall	
0% (0.00–0.56)	> Spain (probable FA) – EuroPrevall	
0% (0.00–0.88)	> Greece (probable FA) – EuroPrevall	
Adults		
0% (0.00–0.25) out of 17 295	> Switzerland (probable food allergy) – EuroPrevall	Lyons *et al.*, 2019
0% (0.00–0.21) out of 17 295	> Netherlands (probable FA) – EuroPrevall	Lyons *et al.*, 2019
0% (0.00–0.36) out of 17 295	> Lithuania (probable FA) – EuroPrevall	
0% (0.00–0.28) out of 17 295	> Iceland (probable FA) – EuroPrevall	
0% (0.00–0.44) out of 17 295	> Spain (probable FA) – EuroPrevall	
0% (0.00–0.68) out of 17 295	> Greece (probable FA) – EuroPrevall	

A3.2.4.2 Mustard

TABLE A38 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> Prevalence data based on food challenges for mustard allergy are scarce owing to the difficulty of masking the strong taste of mustard and to the severity of systemic reactions reported following ingestion of mustard in allergic individuals (EFSA, 2014).

> There is no meta-analysis available for the prevalence of mustard allergy.

> Most of the prevalence studies in unselected populations have been published in Europe where mustard is on the list of priority allergens. Prevalence in unselected populations has been investigated also in India (Mahesh *et al.*, 2016).

> A prevalence of 0.03 percent based on a probable diagnosis of mustard allergy has been reported in Poland (grade 2) but not found in five other European countries (Lyons *et al.*, 2019).

> Prevalence of mustard allergy has been generally reported in selected populations, either in patients recruited at hospital or in atopic individuals (grade 4).

> At the end of the 1990s, mustard allergy was reported to be the fourth leading cause of food allergy in France after milk, eggs and peanuts based on OFC and SPT but in a selected population of children with "food hypersensitivity" (Rancé *et al.*, 2000). No recent data has been published to confirm the importance of mustard allergy in France.

TABLE A39 **AGE GROUP SUMMARY FEEDING INTO DECISION (Based on grade 1 data)**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	Insufficient data to determine low or high	**Very low**	**Low**	Mixed	High

TABLE A40 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Infants		
No data		
School-age children		
No data		
Adults		
No data		

TABLE A40 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Infants		
No data		
School-age children (IC95%)		
0% (0–0.49%)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2020
0% (0–0.86%)	> Lithuania (EuroPrevall)	
0% (0–0.56%)	> Spain (EuroPrevall)	
0% (0–0.37%)	> Poland (EuroPrevall)	
0% (0–0.37%)	> Netherlands (EuroPrevall)	
0%	> Greece (EuroPrevall)	
Adults (IC95%)		
0% (0–0.25%)	> Switzerland (EuroPrevall)	Lyons *et al.*, 2019
0% (0–0.28%)	> Iceland (EuroPrevall)	
0% (0–0.44%)	> Spain (EuroPrevall)	
0.03% (0–0.52%)	> Poland (EuroPrevall)	
0% (0–0.21%)	> Netherlands (EuroPrevall)	
0% (0–0.68%)	> Greece (EuroPrevall)	

A3.2.4.3 Sesame

TABLE A41 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

SUMMARY

> Considering the prevalence in infants of grade 1 and grade 2, there are three regions with 0.4 percent up to 0.72 percent (Middle East [Israel], Australia [Melbourne], and the United States of America) sesame allergy. The prevalence overfulfils criteria for bin 2 but does not fall into criteria for bin 3 as no region had a prevalence in any age group > 1.0 percent. Therefore, the prevalence of sesame allergy was assigned to bin 2.

> The rate of coexistent peanut, tree nut and sesame seed allergy in a European outpatient clinic population is 60.7 percent (Brough *et al.*, 2020).

> Fat-soluble oleosins are also responsible for allergic reactions and may be relevant to severe anaphylaxis but appear to be under-represented in extracts used for SPT and determination of sesame specific IgE (Zuidmeer-Jongejan *et al.*, 2014; Patel and Bahna, 2016; Adatia *et al.*, 2017).

TABLE A42 **AGE GROUP SUMMARY FEEDING INTO DECISION (Based on grade 1 data)**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	Insufficient data to determine low or high	**Very low**	**Low**	Mixed	High

TABLE A43 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
No data		
Infants		
Israel 0.72% (confirmed FA by open food challenge)	> Mean age of 22.4 months; n = 1 923 in Israel	Garkaby *et al.*, 2021
Australia 0.6% (95% CI 0.5–0.9)	> Prevalence at age 1 year old in Melbourne	Peters *et al.*, 2017
Australia 0.4% (95% CI 0.3–0.6)	> Prevalence at age 4 years old in Melbourne	Peters *et al.*, 2017
School-age children		
Australia 0.1%	> Probable allergy to sesame was 0.2% with 44% challenge positivity.	Sasaki *et al.*, 2018
Adults		
Israel 0.09% (confirmed FA by open food challenge)	> Age 17 to 18 years old; total number of participants: 12 592 in Israel	Nachshon *et al.*, 2019

TABLE A43 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants		
Israel: 0.18% (16 out of 9 070)	> Mean age: 10.5 months (6 to 21 months); high number of anaphylaxis reports for sesame in Israel	Dalal *et al.*, 2002
School-age children		
Canada: 0.03% (95% CI 0–0.06)	> Convincing history + physician confirmed + SPT/IgE	Ben-Shoshan *et al.*, 2010
Adults		
Canada: 0.01% (95% CI 0–0.02)	> Convincing history + physician confirmed + SPT/IgE	Ben-Shoshan *et al.*, 2010

A3.2.5 TREE NUTS

A3.2.5.1 Almond

TABLE A44 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> Data on the prevalence of almond allergy are sparse and the rate varies between 0–0.3% in grade 1 and grade 2 studies and only in school-age children. On this basis and considering the restricted regions from which the data come, the prevalence of almond allergy was considered to be in bin 1 (very low).

> No meta-analysis has been performed specially for almond allergy.

TABLE A45 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	**Low**	Mixed	High

TABLE A46 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
Not available		
Infants		
No data		
School-age children		
0%; 0/324 – Iceland; 0–328 – Sweden	> Questionnaires, SPTs, challenges of any positives	Kristjansson *et al.*, 1999
Australia 0.3% (95% CI, 0.1% to 0.5%)	> Challenge-confirmed 6- year-olds	McWilliam *et al.*, 2019
Australia 0% (0/5 016)	> Challenge-confirmed school children	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A46 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
Non available		
Infants		
No data		
School-age children		
0.2% (2/969)	The United Kingdom Isle of Wight birth cohort age 6 – Two children had a possible food allergy, one of whom was challenged and was negative; the other declined the challenge.	Venter *et al.*, 2006

A3.2.5.2 Brazil nut

TABLE A47 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> Brazil nut allergy appears to be restricted to the United Kingdom and Australia, possibly reflecting food consumption patterns and only based on three studies with insufficient data available for prevalence in infants or adults. Even though the prevalence in the studies available suggest it is low, the restricted nature of the data meant the consensus was to classify it as very low with a strong regional restriction.

> Only a limited number of studies have investigated the prevalence of Brazil nut allergy and only two that have challenge-proven the allergy. Therefore, it is not possible to draw any conclusions as to differences in prevalence around the world or as a function of age group. This is also the reason why there are no meta-analyses available.

> There are no data on infants and young children, but this is likely because tree nuts are not recommended for consumption in this age group.

> There is a view that Brazil nut allergy is limited to certain geographies where Brazil nut is more widely consumed, such as the United Kingdom (Arshad *et al.*, 1991). However, there, the epidemiological data to confirm this is either weak or lacking.

> Evidence from a pan-European outpatient clinic study shows that it may be a cause of severe reactions during OFC although the low study subject numbers are a confounding factor (Brough *et al.*, 2020).

TABLE A48 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	**Low**	Mixed	High

TABLE A49 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants (Change age categories as appropriate if needed)		
No data		
School-age children		
Australia 0.02%	> Total clinic study population = 5 016 > Of clinic-diagnosed Brazil nut allergies, only 1 had a positive OFC (25%).	Sasaki *et al.*, 2018
Adults		
None		

TABLE A49 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants (Change age categories as appropriate if needed)		
None		
School-age children		
the United Kingdom 2/891 = 0.2%	> Unclear if subjects had a food challenge	Venter *et al.*, 2008
Australia 0.4%	> Total age 6 follow-up = 1 117. > 5 subjects defined as Brazil-nut allergic; unclear if these are challenge proven.	McWilliam *et al.*, 2019
Adults		
No data		

A3.2.5.3 Cashew nut

TABLE A50 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	**Mixed**	High

SUMMARY

> Only a limited number of studies have investigated prevalence of Cashew-nut allergy, two that include a challenge-proven food allergy in Australia and one pan-European study. These indicate divergent rates spanning three orders of magnitude. It is also the reason why there are no meta-analyses available.

> The data indicated that the prevalence of cashew-nut allergy fell into bin 3 since rates of allergy were > 1 percent in at least one region.

> There are data indicating that cashew-nut allergy is closely related to pistachio allergy because of the close botanical relatedness of these nuts. Thus, co-existent allergy OR 585.2 (95% CI 31.7– > 9999.9) was observed in a pan-European study of 122 subjects (mean age five years old) (Brough *et al.*, 2020).

> The allergy appears to affect young children and adults.

TABLE A51 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	Very low	Low	**Mixed**	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	**Mixed**	High
Adults	Insufficient data to determine low or high	Very low	Low	**Mixed**	High

TABLE A52 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants (Change age categories as appropriate if needed)		
Australia 1.1%	> OFC confirmed food allergy (48 of 4 291 subjects aged 4); data are in Suppl Table E2 where 80 possible cashew allergic subjects were evaluated including OFC with 48 having a positive OFC.	Peters *et al.*, 2017
School-age children		
Australia 0.4%	> Total clinic study population = 5 016 > Of clinic-diagnosed cashew-nut allergies, only 22 had a positive OFC (26.8%).	Sasaki *et al.*, 2018
Australia 2.7% (95% CI, 2.2% to 3.3%)	> Definite food allergy which was confirmed by OFC (121 of 5 276 subjects aged 6)	McWilliam *et al.*, 2019
Europe 0.01%	> iFAAM-EuroPrevall birth cohort follow-up unselected study population school-age children (8 years old). 2 OFC adverse reactions out of 6 069	Grabenhenrich *et al.*, 2020
Adults		
No data		

TABLE A52 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants (Change age categories as appropriate if needed)		
the United Kingdom 1/891 = 0.1%	Study in young children 3 years of age in the United Kingdom	Venter *et al.*, 2008
School-age children		
the United Kingdom 2/891 = 0.2%	> Unclear if subjects had a food challenge	Venter *et al.*, 2008
Adults		
No data		

A3.2.5.4 Coconut

TABLE A53 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

SUMMARY

> The prevalence of coconut allergy has not been defined in unselected populations, for any age group or any region.

> Coconut is a monocotyledenous plant, whereas other tree nuts are dicotyledenous, so likelihood of cross reactivity should be diminished.

TABLE A54 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

A3.2.5.5 Hazelnut

TABLE A55 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	**Mixed**	High

SUMMARY

> Prevalence of hazelnut allergy, however it is defined, is higher in children and adults than in infants.

> Prevalence is higher in countries such Lithuania and very low in inland China and rural South Africa.

> The pattern of allergy may be linked in part with the patterns of birch-pollen related hazelnut. Hazelnut allergy can exist in both a milder form associated with sensitization to birch pollen as well as a form that is associated with more severe reactions associated with sensitization to storage proteins and lipid transfer proteins (Datema *et al.*, 2015). It appears to be associated with other tree nuts allergies such as walnut and pecan (Brough *et al.*, 2020).

TABLE A56 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	**Mixed**	High
Adults	Insufficient data to determine low or high	Very low	Low	**Mixed**	High

TABLE A57 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants		
South Africa 0.0%	Ages were: >26 months (urban), 21 months (rural) >Study population reflects ethnicity in Cape Town. >Allergy rates in the rural population were too low to calculate prevalence of food allergy.	Botha *et al.*, 2019
Australia 0.16%	>Prevalence at age 4 years old in Melbourne. Seven positive OFC to hazelnut out of 4 291 = 0.16% at age 4 years old	Peters *et al.*, 2017
School-age children		
Europe 0.33%	>Prevalence at mean age 8.3 years (8 EU countries)	Grabenhenrich *et al.*, 2020
Australia 0.04%	>2 challenge proven hazelnut allergic subjects from 5 016 = 0.04%	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A57 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants		
No data		
School-age children		
2.15 (0.41–5.26) (Vilnius) 0.07 (0.03–0.63) (Reykjavik)	>Prevalence in school-age children mean age ~9 years old >pan-European	Lyons *et al.*, 2020
0.00 (0.00–0.06) (China, Hong Kong SAR) 0.05 (0.02–0.11) (Tomsk)	>Prevalence in school-age children mean age ~8–10 years old >China, India and Russian Federation	Li *et al.*, 2020
Adults		
2.57 (1.47–4.02) (Zurich) 0.06 (0.19–0.99) (Athens)	>Prevalence in adults median age ~36 years old	Lyons *et al.*, 2019

A3.2.5.6 Macadamia nut

TABLE A58 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> A bin 1 classification was decided upon because only two studies fulfilling the requirements for grade 1 and 2 data were available. These studies are from one region (Australia), and one of them had zero challenge positive rate.

> That evidence indicates Macadamia nut allergy is uncommon. A pan-European study of co-existent tree nut allergies (mean age five years old) indicated that Macadamia nut allergy was only found in the children with multiple (> 3) tree nut allergies. Symptom severity during OFC has proportionally more involvement of the lower respiratory tract and/or cardiovascular/neurological system than other nuts, although this observation maybe confounded by low study subject numbers (Brough *et al.*, 2020).

> There are no data on infants and young children, but this is likely because tree nuts are not recommended for consumption in this age group.

TABLE A59 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

TABLE A60 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
None		
School-age children		
0.0%	> Total study population = 5 016 > 11 of probable food-allergic subjects gave total confirmed > Macadamia nut allergies by oral food challenge = 0	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A60 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
No data		
School-age children		
Australia 1.0%	> Total in age 6 follow-up = 1 117 > Macadamia nut clinic confirmed foods allergy = 11 (these were not challenge-proven).	McWilliam *et al.*, 2019
Adults		
No data		

A3.2.5.7 Pecan

TABLE A61 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> Walnut and pecan are closely related botanically with the allergens having a high level of sequence identity and similarity. Allergies to the two tree nuts are similarly closely allied and as shown in a multi-centre OFC study in Europe they are co-existent (OR 150.6 95 percent CI 18.5–1228.3) (Brough *et al.*, 2020).

> Challenge-proven pecan allergy shows a variation in prevalence between 0.02–0.04 percent in children in Australia fulfilling the criteria for being classified as being in bin 1.

> The prevalence of pecan allergy is lower than that of walnut and its distribution may be related to consumption patterns.

> Data are sparse on the prevalence of pecan allergy, which means it is not possible to assess whether the rate of allergy changes with age or geography.

TABLE A62 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	**Insufficient data to determine low or high**	Very low	Low	Mixed	High

TABLE A63 **EVIDENCE**

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
Australia 0.02%	OFC confirmed food allergy (1 of 4 291 subjects aged 4 years old)	Peters *et al.*, 2017
School-age children		
Australia 0.04%	> Total clinic study population = 5 016 > Of clinic-diagnosed pecan allergies, only 2 had a positive OFC (22.2%).	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A63 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
No data		
School-age children		
Australia 0.2%	> Total clinic study population = 5 016 > Total clinic-diagnosed pecan allergies = 9	Sasaki *et al.*, 2018
Adults		
No data		

A3.2.5.8 Pine nut

TABLE A64 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

SUMMARY

> There is little epidemiological evidence, but what is published shows pine nut allergy to be in a very low prevalence category (0–0.2 percent).

> Evidence comes from Australia, Mexico and Europe, seems to indicate that it is a regional allergen – specific to Australia (0.01 percent in infants and 0.1–0.2 percent in school-age children).

TABLE A65 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Adults	Insufficient data to determine low or high	**Very low**	Low	Mixed	High

TABLE A66 EVIDENCE

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants		
Australia 0.01%	One subject in the 4 years-old age group follow-up of HealthNuts cohort (1/4 291) had OFC confirmed food allergy to pine nut.	Peters *et al.*, 2017
School-age children		
0%; 0/324 – (Iceland) 0–328 – (Sweden)	> Questionnaires, SPTs, challenges of any positives. Sweden and Iceland	Kristjansson *et al.*, 1999
0.1% (4/5 016) challenge-confirmed school-age children.	> Australia	Sasaki *et al.*, 2018
Adults		
No data		

TABLE A66 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None available		
Infants		
No data		
School-age children		
0.2% (11/5 276) challenge-confirmed 6-year-olds	> Australia	McWilliam *et al.*, 2019
Adults		
0%; 0/1 126 unselected adults	> Mexico	Bedolla-Barajas *et al.*, 2015

A3.2.5.9 Pistachio

TABLE A67 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	Low	**Mixed**	High

SUMMARY

> There are data indicating that pistachio allergy is closely related to cashew allergy because of the close botanical relatedness of these nuts. The study also indicated pistachio nut allergy was only observed in the context of multiple tree nut allergies in children with three or more tree nut allergies (Brough *et al.*, 2020).

> Only a limited number of studies have investigated prevalence of pistachio nut allergy and only three that have challenge-proven food allergy, two of which were from Australia and one from Turkey. Therefore, it is not possible to draw any conclusions as to differences in prevalence around the world or as a function of age group. It is also the reason why there are no meta-analyses available.

> Data from studies confirming food allergy with OFC and self-reported allergies indicate it is a significant allergy in terms of prevalence in Australia and the United States of America.

> The allergy appears to affect young children and adults.

TABLE A68 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	**Insufficient data to determine low or high**	Very low	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	Low	**Mixed**	High
Adults	Insufficient data to determine low or high	Very low	Low	Mixed	High

TABLE A69 EVIDENCE

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
No data		
School-age children		
Australia 0.08%	> Total clinic study population = 5 016 > Of clinic-diagnosed pistachio nut allergies, 4 had a positive OFC (8.6%; cf. Table V).	Sasaki *et al.*, 2018
Turkey 0.1%	> One subject with confirmed allergy to pistachio out of 1 139 school-age children	Kaya *et al.*, 2013
Adults		
None		

TABLE A69 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
No data		
School-age children		
Australia 0.9%	> Definite food allergy but pistachio allergy was not confirmed by OFC (50 of 5 276 subjects). > Challenges were done for cashew, and the concordance between the two allergies means both would not have been confirmed by OFC.	McWilliam *et al.*, 2019
Adults		
None		

A3.2.5.10 Walnut

TABLE A70 **OVERALL SCORE**

GROUP	0	1	2	3	4
PREVALENCE (Decision for matrix)	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

SUMMARY

> Walnut and pecan are closely related botanically with the allergens having a high level of sequence identity and similarity. Allergies to the two tree nuts are similarly closely allied and have shown through a multi-centre OFC study in Europe to be co-existent (OR 150.6 95 percent CI 18.5–1228.3) (Brough *et al.*, 2020).

> Challenge-proven walnut allergy shows a variation in prevalence of between 0.1–0.02 percent in children in Europe and Australia.

> Prevalence of probable food allergy suggests it is higher in Europe and Australia than in India or East Asia.

TABLE A71 **AGE GROUP SUMMARY FEEDING INTO DECISION**

GROUP	0	1	2	3	4
Infants and young children ≤ 3 years old	Insufficient data to determine low or high	**Very low**	Low	Mixed	High
Children 4–18 years old	Insufficient data to determine low or high	Very low	**Low**	Mixed	High
Adults	Insufficient data to determine low or high	Very low	**Low**	Mixed	High

TABLE A72 EVIDENCE

GRADE 1	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
0.12%	OFC confirmed food allergy (5 of 4 291 subjects aged 4) Healthnuts cohort	Peters *et al.*, 2017
School-age children		
Australia 0.02%	> Total clinic study population = 5 016 > Of clinic-diagnosed walnut allergies, only 8 had a positive OFC (23.5%).	Sasaki *et al.*, 2018
Europe 0.02%	> iFAAM-EuroPrevall birth cohort follow-up unselected study population school-age children (8 years old) > One OFC adverse reaction to walnut out of 6 069	Grabenhenrich *et al.*, 2020
Turkey 0.04%	> 4/10 096 reacted on OFC in Turkey, mean age 13 years old	Kaya *et al.*, 2013
Adults		
None		

TABLE A72 **EVIDENCE** (continued)

GRADE 2	COMMENTS	REFERENCE
Meta-analysis		
None		
Infants		
No data		
School-age children		
Argentina 0.01%	> 3/23 733; only two cases were identified in ages 3–5 and one in ages 12–18. > It is not clear from the paper (which is in Spanish) if it refers to walnut or simply tree nuts. > Study in Argentina	Petriz *et al.*, 2020
Australia 0.25%	> Total age 6 follow-up =1 117 > 28 subjects defined as walnut allergic	McWilliam *et al.*, 2019
0.00%	> Prevalence at age 6–11 years old in 5 cities/ regions/areas in China (Hong Kong SAR, > Guangzhou and Shaoguan), India (Bengaluru and Mysore) and Russian Federation (Tomsk)	Li *et al.*, 2020
> 0.27, Zurich, Switzerland > 0.53, Madrid, Spain > 0.56, Athens, Greece > 0.48, Lodz, Poland > 0.53, Utrecht, Netherlands > 0.00, Reykjavik, Iceland > 0.00, Vilnius, Lithuania	> EuroPrevall child study	Lyons *et al.*, 2020
Adults		
> 0.58, Zurich, Switzerland > 0.71, Madrid, Spain > 0.29, Athens, Greece > 0.15, Lodz, Poland > 0.10, Utrecht, Netherlands > 0.05, Reykjavik, Iceland	> EuroPrevall adult study	Lyons *et al.*, 2019

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ANNEX 4
POTENCY CRITERIA DECISION AND SUPPORTING INFORMATION FOR INDIVIDUAL FOODS[5]

During this first meeting, these tables were used to facilitate the discussion regarding the priority list. The data sources utilized will be further discussed and used for the second meeting and reporting of potential thresholds/reference doses. For additional details, please see the main text of the second report as well as its Annex for the 71 studies considered in addition to the data sources used by Remington *et al.* (2020) and Houben *et al.* (2020).

[5] Text and figures in **bold** in the following tables indicate applicable values.

TABLE A73 **MILK**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	> 1 000 mg protein	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was overwhelmingly paediatric, with data available from 11 countries in three regions (Europe [including Turkey], North and South America) > 123 of 450 available data points were right or left censored, with 27 being right censored and 96 being left censored; 18 of 450 available data points were from adults.				
Number of studies available for dose distribution modelling	n = 21			
Number of individual data points available for dose distribution modelling	n = 450			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		High	Adequate	**Low (children)**
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	Adequate (n = ~40–100)	**Good (n ≥ 100)**

Considerations for risk management discussion: N/A

TABLE A74 **EGG**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	> 1 000 mg protein	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was overwhelmingly paediatric, with data available from 14 countries in two regions (Europe [including Turkey] and North America). > 99 of 431 available data points were right or left censored; 12 of 431 available data points were from adults.				
Number of studies available for dose distribution modelling	n = 18			
Number of individual data points available for dose distribution modelling	n = 431			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		High	Adequate	**Low (children)**
Quantity of data available for dose distribution modelling	not available (n =)	Poor (n ≤ 40)	Adequate (n = ~40–100)	**Good (n ≥ 100)**

Considerations for risk management discussion: N/A

TABLE A75 **PEANUT**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	> 1 000 mg protein	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was about 85% paediatric, with data available from 13 countries in three regions (Europe, North America and Asia pacific [Australia]). > 336 of 1 306 available data points were right or left censored, with 275 being right censored and 61 being left censored; 18 of 450 available data points were from adults.				
Number of studies available for dose distribution modelling	n = 27			
Number of individual data points available for dose distribution modelling	n = 1 306			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		High	**Adequate**	Low
Quantity of data available for dose distribution modelling	not available (n =)	Poor (n ≤ 40)	Adequate (n = ~40–100)	**Good (n ≥ 100)**

Considerations for risk management discussion: N/A

TABLE A76 **SOYBEAN**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM/LOW			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	**> 100 mg protein**	**10–100 mg protein**	1–10 mg protein	< 1.0 mg protein
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	10–100 mg protein	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from children and adults, with data available from four countries in two regions Europe (Italy, Switzerland, Germany and Netherlands) and North America. > 39 of 87 available data points were right or left censored, with 33 being right censored and six being left censored.				
Number of studies available for dose distribution modelling	n = 9			
Number of individual data points available for dose distribution modelling	n = 87			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	Good (n ≥ 100)

Considerations for risk management discussion: N/A

TABLE A77 **WHEAT**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	> 1 000 mg protein	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was about 85% paediatric, with data available from eight countries in two regions (Europe and Asia). > 11 of 99 available data points were right or left censored, with two being right censored and nine being left censored.				
Number of studies available for dose distribution modelling	n = 9			
Number of individual data points available for dose distribution modelling	n = 99			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	**Adequate**	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	**Good (n ≥ 100)**

Considerations for risk management discussion: N/A

TABLE A78 **OTHER CEREALS**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A79 **MUSTARD**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	HIGH (See **Considerations for risk management discussion**)			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	10–100 mg protein	**1–10 mg protein**	**< 1.0 mg protein**
ED50 mg range, including 95% CI	> 1 000 mg protein	**100–1 000 mg protein**	**10–100 mg protein**	**< 10 mg protein**
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from children and adults, with data available from Europe (Spain and France). > 12 of 33 available data points were right or left censored, with 10 being right censored and two being left censored.				
Number of studies available for dose distribution modelling	n = 3			
Number of individual data points available for dose distribution modelling	n = 33			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	**Poor (n ≤ 40)**	Adequate (n = ~40–100)	Good (n ≥ 100)

CONSIDERATIONS FOR RISK MANAGEMENT DISCUSSION:

The 95 percent confidence intervals for one or both the mustard ED10 and ED50 estimates overlap with the 95 percent confidence intervals for cashew, celery, egg, hazelnut, lupin, milk, peanut, sesame, walnut and wheat. Thus, while the potency decision is labelled as "high", there is a large level of overlap between mustard and the food designated "medium" potency.

Additionally, the highest discrete doses of mustard in the three studies providing individual data for dose distribution modelling were relatively low compared to other food-challenge protocols for common food allergens (ending above 1 000 mg of protein). This low dosing scheme for mustard resulted in a high proportion of right-censored results which could impact the resulting dose distribution, particularly in the ED50 range and above when compared to other foods. This results in a potential high bias in the available data.

Highest discrete dose (rounded to nearest 5 mg for ease of reading):

> About 80 mg mustard protein (Morisset *et al.*, 2003)
> About 130 mg mustard protein (Rancé *et al.*, 2000)
> About 235 mg mustard protein (Figueroa *et al.*, 2005)

TABLE A80 **BUCKWHEAT**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	High
Quantity of data available	Poor

Considerations for risk management discussion: N/A

TABLE A81 **KIWI**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	High
Quantity of data available	Poor

Considerations for risk management discussion: N/A

TABLE A82 **FISH**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	1–10 mg protein	< 1.0 mg protein
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	10–100 mg protein	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from children and adults, with data available from Europe (Iceland, Greece, France, Spain, Lithuania, Denmark, Norway and Netherlands) and the United States of America. > 15 of 82 available data points were right or left censored, with 10 being right censored and five being left censored. > Available data was from a limited number of species.				
Number of studies available for dose distribution modelling	n = 5			
Number of individual data points available for dose distribution modelling	n = 82			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		High	**Adequate**	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	Good (n ≥ 100)

Considerations for risk management discussion: N/A

TABLE A83 **CRUSTACEAN (Shrimp; all others N/A)**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	LOW			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	**> 100 mg protein**	10–100 mg protein	1–10 mg protein	0.1–1.0 mg protein
ED50 mg range, including 95% CI	**> 1 000 mg protein**	100–1 000 mg protein	10–100 mg protein	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was overwhelmingly adults, with data available from five countries in two regions (Europe and North America). > 38 of 75 available data were being right censored; 2 of 75 available data points were from children. > Available data was from a limited number of species.				
Number of studies available for dose distribution modelling	n = 4			
Number of individual data points available for dose distribution modelling	n = 75			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	Good (n ≥ 100)

Considerations for risk management discussion: N/A

TABLE A84 **HAZELNUT**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	10–100 mg protein	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from children and adults, with data available from 12 countries in Europe distributed across region. > 214 of 411 available data points were right or left censored, with 205 being right censored and nine being left censored.				
Number of studies available for dose distribution modelling	n = 10			
Number of individual data points available for dose distribution modelling	n = 411			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		High	**Adequate**	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	Adequate (n = ~40– 100)	**Good (n ≥ 100)**

Considerations for risk management discussion: N/A

TABLE A85 **BRAZIL NUT**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A86 **MACADAMIA**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A87 **CASHEW NUTS**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	**< 1.0 mg protein**
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was paediatric, with all available data available from Netherlands (two centres). > 128 of 245 available data points were right or left censored.				
Number of studies available for dose distribution modelling	n = 3			
Number of individual data points available for dose distribution modelling	n = 245			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	Adequate (n = ~40–100)	**Good (n ≥ 100)**

Considerations for risk management discussion: N/A

TABLE A88 **PISTACHIO**

Potency decision (Low/Med/High)	N/A (cross with cashew)
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A89 **WALNUTS**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	**< 1.0 mg protein**
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from adults and children, with data available from one country (Netherlands). > 36 of 74 available data were right or left censored, with 31 right censored and five left censored.				
Number of studies available for dose distribution modelling	n = 2			
Number of individual data points available for dose distribution modelling	n = 74			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	Good (n ≥ 100)

Considerations for risk management discussion: N/A

TABLE A90 **ALMOND**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A91 **CHESTNUTS**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A92 **PECAN**

Potency decision (Low/Med/High)	N/A (cross with walnut)
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: According to Elizur *et al.* (2019), the majority of individuals with co-allergy in a study undergoing walnut immunotherapy were also reactive to pecan during oral food challenge, although the median reactive dose for pecan nuts allergic individuals was higher than the median reactive dose for these individuals to react to walnut.

TABLE A93 **PINE NUTS**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A94 **COCONUT**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A95 **SESAME**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	**> 100 mg protein**	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from children and adults, with data available from Europe (France and Netherlands). > 13 of 40 available data points were right or left censored, with 10 being right censored and three left censored.				
Number of studies available for dose distribution modelling	n = 4			
Number of individual data points available for dose distribution modelling	n = 40			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	Not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	Good (n ≥ 100)

Considerations for risk management discussion: N/A

TABLE A96 **CELERY**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	> 100 mg protein	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	> 1 000 mg protein	**100–1 000 mg protein**	**10–100 mg protein**	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was mostly adults, with data available from Central Europe (Switzerland, Germany, Italy, France and Poland; one from Netherlands). > 32 of 82 available data points were right or left censored, with 18 being right censored and 14 being left censored.				
Number of studies available for dose distribution modelling	n = 4			
Number of individual data points available for dose distribution modelling	n = 82			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	Poor (n ≤ 40)	**Adequate (n = ~40–100)**	Good (n ≥ 100)

Considerations for risk management discussion: N/A

TABLE A97 **MOLLUSCAN SHELLFISH**

Potency decision (Low/Med/High)	N/A
Potential biases of data available	N/A
Quantity of data available	N/A

Considerations for risk management discussion: N/A

TABLE A98 **LUPIN**

POTENCY DECISION (LOW/MED/HIGH) (Criteria decision for inclusion on global priority allergen list)	MEDIUM			
Supporting information				
Potency	**Bin 1**	**Bin 2**	**Bin 3**	**Bin 4**
ED10 mg range, including 95% CI	**> 100 mg protein**	**10–100 mg protein**	**1–10 mg protein**	< 1.0 mg protein
ED50 mg range, including 95% CI	**> 1 000 mg protein**	**100–1 000 mg protein**	10–100 mg protein	< 10 mg protein
Summary of data sources used by Remington *et al.* (2020) and Houben *et al.* (2020), and origins (demographic, medical/clinical and geographic)				
> The available data was from children and adults, with data available from Europe (Italy, France, the United Kingdom and Netherlands). > 10 of 25 available data were right or left censored, with nine being right censored and one being left censored.				
Number of studies available for dose distribution modelling	n = 4			
Number of individual data points available for dose distribution modelling	n = 25			
Expert consultation review: assessment of potential biases of available data and data quantity for dose distribution modelling				
Potency		**Bin 1**	**Bin 2**	**Bin 3**
Potential biases of available data		**High**	Adequate	Low
Quantity of data available for dose distribution modelling	not available n/a (n =)	**Poor (n ≤ 40)**	Adequate (n = ~40– 100)	Good (n ≥ 100)

Considerations for risk management discussion: N/A

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QUINOA
SEME DI
SESAMO

RISK ASSESSMENT OF FOOD ALLERGENS
PART 1: REVIEW AND VALIDATION OF CODEX ALIMENTARIUS PRIORITY ALLERGEN LIST THROUGH RISK ASSESSMENT

MEETING REPORT

The labelling of food allergens in pre-packaged foods plays a key role in protecting food allergic individuals, as no preventative clinical treatment is currently available. The list of major foods and ingredients known to cause hypersensitivity was included into the Codex General Standard for the Labelling of Packaged Foods (GSLPF) in 1999. There have been many scientific developments in the understanding of food allergens and their management since the original drafting of the GSLPF. Thus, in response to the request from Codex for scientific advice, including current evidence of consumer understanding of allergens, FAO and WHO convened a series of three expert meetings to provide scientific advice on this subject.

The purpose of the first meeting of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens was to review and validate the Codex priority allergen list through risk assessment. This report focuses on the deliberations and conclusions of this meeting.

FOOD SYSTEMS AND FOOD SAFETY - ECONOMIC AND SOCIAL DEVELOPMENT
WEBSITE: WWW.FAO.ORG/FOOD-SAFETY
FOOD AND AGRICULTURE ORGANIZATION OF THE UNITED NATIONS
ROME, ITALY

DEPARTMENT OF NUTRITION AND FOOD SAFETY
WEBSITE: WWW.WHO.INT/HEALTH-TOPICS/FOOD-SAFETY
WORLD HEALTH ORGANIZATION
GENEVA, SWITZERLAND

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