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Proposed reference doses for food allergens – the science behind and risk groups

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Preface

This risk assessment report summarises the opinion of an ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens and further characterises the potential implications for allergic Swedish and European consumers. The report was requested by The Swedish Food Agency (SFA) risk management departments SV/EUSE and UV/HM (Dnr 2022/01168). The FAO and WHO expert group opinion may lead to a revised Codex allergen list, reference doses for food allergens and criteria for Precautionary Allergen Labelling. The Swedish Food Agency therefore needs to understand e.g. the evidence behind the reference doses and how the Swedish/European perspective was considered in the reports from the FAO/WHO expert group.

This report starts with a summary of the FAO and WHO expert committee outcomes followed by a hazard identification and characterisation, an exposure assessment and finally the risk characterisation, in which the specific questions from the risk managers are answered.

Sanna Lignell, toxicologist and Jakob Ottoson, microbiologist, risk assessors at the Risk and benefit assessment department are responsible for the report. Sara Gunnare, toxicologist at the Risk and benefit assessment department and Eva Södergren, Global Sr Scientific Advisor Allergy, Thermo Fisher Scientific, have reviewed it.

Helena Brunnkvist, Head of the Risk and benefit assessement department

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Background

The majority of food allergic reactions is caused by a limited number of food allergens e.g. milk, egg, peanuts, tree nuts and shellfish (crustaceans and molluscs). Information and labelling of food allergens are regulated by Regulation (EU) no 1169/2011[1]. The most common food allergens in the EU region are listed in annex II to the regulation (Table 1). Codex Alimentarius is FAO/WHO's organ for food standards, guidelines and codes of practice which contribute to the safety, quality and fairness of international food trade. In the Codex General Standard for the Labelling of Prepackaged Foods CXS 1-1985 (GSLPF), food allergens are also listed (Table 1). This allergen list reflects a global perspective and differ from the list in Regulation (EU) no 1169/2011.

Allergens can occur in foods due to unintended cross contamination. Within Regulation (EC) no 852/2004[2] allergens are described as hazards. However, currently there are no thresholds for food allergens. Additionally, there is no unified approach regarding how risk assessment of food allergens should be performed neither within EU nor globally. Therefore, risk management strategies are not always based on risk with several negative consequences for allergic consumers, food businesses and on food waste.

There are differences in sensibility between allergic consumers and to which amount of allergen protein they react. Dose-response relationships have been described based on NOAELs (no observed adverse effect levels) and LOAELs (lowest observed adverse effect levels) from DBPCFCs (double blind placebo-controlled food challenges) data on a population level, showing the higher the dose of protein the larger proportion of allergic individuals will react. An analytical result to a certain food can be recalculated to a dose which can be compared to an eliciting dose to assess the risk for allergic consumers. Such risk assessment can be used as a basis for e.g. hygiene measures and precautionary allergen labelling. How calculations can be performed and thus risk assessment is described in the Risk assessment guide published by the Swedish Food Agency (Livsmedelsverket 2022).

Work related to labelling of food allergens, reference doses for food allergens and Precautionary Allergen Labelling is being conducted within the Codex Committee on Food Labelling (CCFL). An expert group assigned by FAO/WHO has published reports[3] regarding a review of the priority allergens list based on prevalence, severity and potency of specific food allergens, reference doses and evidence in support of Precautionary Allergen Labelling.

Sweden has a long and successful practice when it comes to regulatory issues connected to food allergens in both the Codex and the EU context. An electronic working group (eWG) – Allergen Labelling - within CCFL prepares the discussion for the upcoming 47th CCFL meeting. The mandate of the eWG is to prepare proposed revision to the GSLPF and draft guidelines on Precautionary Allergen Labelling (PAL). The agenda item allergen labelling deals with two important topics;

[1] Regulation (EU) No 1169/2011 of the European Parliament and of the Council of 25 October 2011 on the provision of food information to consumers.

[2] Regulation (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs.

[3] https://www.fao.org/food-safety/scientific-advice/food-allergens/en/

(i) Proposed draft revision to the General Standard for the Labelling of Prepackaged Foods and (ii) Proposed draft guidelines on PAL. These discussions will be based on a report from the eWG and government comments collected before the meeting as well as the scientific advice from the FAO/WHO expert consultations. Thus, risk management measures are *e.g.* a revised Codex priority allergen list, reference doses for food allergens and criteria for PAL. Experts at the Swedish Food Agency (SFA) represent Sweden within the eWG as well as in the CCFL and therefore need to understand the science behind the reference doses and how the Swedish/European perspective could be considered in the reports from the FAO/WHO expert group based on the data available. It is important that SFA has the possibility to answer specific questions, based on risk assessments, now and beyond, with a view to achieving the overall objective with this work – revised GSLPF and new guidelines on PAL for the benefit of consumers, food business operators and other bodies.

Overall questions:

Describe the science and the evidence behind the calculations of the global reference doses. Was the Northern European population represented when these doses were calculated? Which risk groups are there among the allergic consumers and how ill can they become? A risk group among allergic consumers might be described as those that will not be protected by the proposed reference doses, i.e. 5 % of those allergic to the specific allergen.

Specific questions:

1. Describe the methods used to calculate reference doses/eliciting doses of food allergens and the suggested global reference doses.
2. Is the Northern European population represented in the data used for calculations of these reference doses/eliciting doses?
3. Which consequences might the proposed reference doses provoke? How many consumers will not be protected and how severely ill can they become? Is there any treatment for consumers that suffer from acute allergic reactions?
4. Describe the food categories that most commonly are contaminated with food allergens.
5. Is it possible, for European food businesses and control authorities, to analyze food allergens in concentrations that correspond to the reference doses?
6. Describe the prevalence of soy allergy in Europe. Also, describe whether severe allergic reactions have been shown to soy in Europe.

Data sources and methods

Literature

In order to be able to answer the specific questions, careful review of the references forming the conclusions of the FAO/WHO expert group (hereafter called "The Expert Committee") on priority allergens and suggested reference doses for these (FAO and WHO 2021a, b and c; 2022a, b and c) was done. The Expert Committee suggested a list of eight priority allergens based on prevalence (globally), severity (proportion of cases of anaphylaxis globally) and potency (defined as the ability to produce reactions at low doses in double blind placebo-controlled food challenges (DBPCFC)). The consequences for the Swedish/European population of the recommended reference doses were estimated based on European prevalence for the specific allergens in question and symptoms reported to low doses from European studies. Furthermore, the Swedish Food Agency reports (Livsmedelsverket 2021; 2022) and the EFSA (European Food Safety Authority) opinion on allergens in food (EFSA 2014), and references therein, have been used. The section about treatment is mainly based on the guidelines for treatment of anaphylaxis developed by the Swedish Association for Allergology (SFFA 2015).

The Swedish Food Agency allergy register

Since 1990, the Swedish Food Agency records reports from medical centres and food inspectors about unexpected allergic reactions. Between 1990 and 2020, 236 incidents were reported (Livsmedelsverket 2021). In the events when reports were accompanied with a positive food analysis for the allergen in question, Eriksson (2019) and Wilhemsson (2019) used this information (between 2003 and 2018) in order to determine the eliciting doses for reactions to cow's milk (n = 42), eggs (n = 17), peanuts (n = 7) and hazelnuts (n= 3). These data were used in order to see how many events, and the severity of these, that could have been caused by exposures to doses lower than recommended reference doses (FAO and WHO 2021b).

Rapid alert system for food and feed

Rapid alert system for food and feed (RASFF) is an EU system in order to notify if a food product can constitute a hazard for human health for example due to a finding of an undeclared allergen or a contamination. Amongst all notifications (n = 76 284) since the system was in place in 1979[4] a primary filtration was done on hazard category "allergen". The allergen notifications (n = 2452) were further filtered according to "product category" and "substance/finding", and the other way around. The most common combinations are listed in predefined tables in the exposure assessment.

[4] However, the first notification due to the hazard category "allergen" was in 1984

Introduction – FAO and WHO's report and conclusions

Following a request from Codex Committee on Food Hygiene (CCFH) and Codex Committee on Food Labelling (CCFL), FAO/WHO formed an Expert Committee to support with risk assessment and scientific advice for the development of the guidance and practice of food allergens. A series of four meetings was held in this ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens during 2020-22. The main purpose of the meetings was to review evidence to:

1. Validate and, if necessary, update the Codex priority allergen list through risk assessment (1st meeting)
2. Establish threshold levels in foods of the priority allergens (2nd meeting)
3. Summarize support of precautionary labelling in foods of the priority allergens (3rd meeting)
4. Establish exemption for the food allergens (4th meeting)

Summary reports from the meetings are available (FAO and WHO 2021a-c, 2022a, 2023), but full reports have so far only been published from the first two meetings (FAO and WHO 2022b, c). The results of the first two meetings are briefly described below. They are also used to answer the specific questions (see section Background). Reviewing of the results from meeting 3 and 4 is outside the scope of this report.

Review of the Codex priority allergen list (1st meeting)

The purpose of the meeting was to validate, and if necessary update the list of priority allergens in the General Standard for the Labelling of Prepackaged Foods (GSLPF) (FAO and WHO 2018) based on risk assessment.

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 priority allergen list (FAO and WHO 2022b). Thus, it was recommended that foods or ingredients such as lactose, sulphite, and food additives will not be included. Furthermore, key criteria that should be used to establish the list were selected, i.e. *prevalence*, *potency* and *severity*. The literature on these key criteria was reviewed for each food currently on the GSLPF list (Table 1) as well as for other foods found on priority allergen lists established in individual countries or regions (e.g. molluscs, mustard, celery, sesame, buckwheat, lupine and others).

Prevalence

Prevalence was defined as the proportion of a defined population known to have experienced an immune-mediated adverse reaction to a specific food (FAO and WHO, 2022). To assess data quality, the Expert Committee graded data in Grade 1-3. Grade 1 prevalence data was based on confirmed allergy determined with "gold standard tools". For IgE-mediated allergy, this meant a clinical history of reaction to food, together with evidence of sensitization to that food (skin prick test and/or food

allergen specific IgE) and a positive oral food challenge. Grade 2 prevalence data was based on probable adverse reactions to a food with symptoms that were consistent with a particular immune-mediated adverse reaction to the food and evidence of a disease biomarker by measurement of sensitization (such as skin prick test and/or food allergen specific IgE). Grade 3 prevalence data was based on self-reported data and a doctor diagnosis or only evidence of IgE sensitization. The Expert Committee only considered grade 1 and grade 2 data because grade 3 data will overestimate prevalence. Most prevalence data defined point prevalence, but in some instances, data quality allowed meta-analyses which have defined lifetime prevalence. Prevalence data was assessed for infants and young children < 4 yrs, children aged 4 - 18 yrs, and adults separately. Furthermore, to evaluate prevalence data with a global perspective, prevalence was classified as "insufficient data", very low (< 0.5 % in one region only or < 0.1 % in all regions), low (< 0.5 % in all regions), mixed (> 1 % in one region and 0.5 – 1.0 % in at least one other region) or high (> 1.0 % in more than one region). Finally, a consensus was arrived over an overall prevalence score.

Overall, cow's milk, hen's egg and peanuts were classified as being of high prevalence, crustacean shellfish (data mainly on shrimp), wheat (coeliac disease), cashew nut, hazelnut and pistachio as mixed prevalence and fish, wheat (IgE mediated food allergy), celery, kiwi, soybean, buckwheat, mustard, sesame, almond, brazil nut, macadamia nut, pecan, pine nut and walnut as low or very low prevalence (FAO and WHO 2022b).

Potency

Potency was defined as the amount of protein from an allergenic food required to cause objective symptoms in a specified proportion of the allergic population (FAO and WHO 2022b). 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. The Expert Committee classified potency as low, medium or high based on ED10s and ED50s, *i.e.* doses of protein predicted to provoke reactions in 10 % and 50 % of the allergic population, respectively. ED10 and ED50 data for allergenic foods was mainly retrieved from Remington et al. (2020) and Houben et al. (2020) (see section "Establishment of threshold levels in food of priority allergens" below). The amount of data available for dose-distribution modelling and the potential for biases that might affect the eliciting doses were also considered in the assessment of potency.

Briefly, the Expert Committee classified the potency of mustard as high, the potency of milk, egg, peanut, hazelnut, cashew nut, wheat (IgE), fish, walnut, sesame, lupin and celery as medium, the potency of soybean as medium/low and the potency of crustacean (data on shrimp) as low. Data for other cereals, buckwheat, kiwi, brazil nut, macadamia, pistachio (cross-react with cashew), almond, chestnuts, pecan nuts (cross-react with walnuts), pine nuts, coconut, crustacean others than shrimp and molluscan shellfish were insufficient for dose-distribution modelling (FAO and WHO 2022b).

Severity

Severity was defined as the frequency or proportion of severe objective reactions (such as anaphylaxis) to a food (FAO and WHO 2022b). Severity was based on a clinical assessment inferred from published clinical studies or other documented evidence of food-induced allergic reactions observed within populations of allergic individuals. Thus, the Expert Committee concluded that this extensive evidence on a population level from different parts of the world may be confounded by differences in definitions of severity and the accuracy of reporting. Allergens were categorized in

groups according to proportions of anaphylaxis in different regions based on data from the systematic review by Bassegio Conrad et al (2021). The groups were A (allergens which cause at least 5 – 10 % of anaphylaxis reactions in ≥ 3 Codex regions), B (allergens which cause at least 5 – 10 % of anaphylaxis reactions in 1 - 2 Codex regions and C (allergens which cause a lower proportion of anaphylaxis reactions in all regions or allergens which cause at least 5 – 10 % of anaphylaxis reactions in only one Codex region, but a lower proportion of anaphylaxis reactions elsewhere. The level of evidence was also considered in the grouping.

In summary, the Expert Committee assigned peanuts, certain tree nuts (walnut, pecan, cashew, pistachio, hazelnut, almond, brazil nut), sesame, wheat, eggs, cow's milk (and other mammalian milk), fish and crustacea/shrimp to group A. Pecan was assigned to group A on basis of cross-reactivity with walnut and other mammalian milk on the basis of cross-reactivity with cow's milk. Pine nuts, macadamia and lupin were assigned to group B and shea nut, coconut, soybean, mustard, buckwheat, celery, mollusca and fruits to group C (FAO and WHO 2022b).

Overall assessment

Based on the systematic assessments of prevalence, severity and potency, the Expert Committee selected allergenic foods to be included on the priority allergen list. A hazard prioritization process was used as a help in the decision. In this process, the criterion-based values of prevalence, severity and potency were normalized, weighted and summed to scores for each food. In a sensitivity analysis, the process was repeated for different weighting options. Irrespective of weighting option, milk, eggs and peanuts got the highest scores, followed by hazelnut, cashew nut, crustacea, wheat (IgE), fish, walnut, sesame and pistachio nut (FAO and WHO 2022b). In addition to the foods with highest scores, pecan nut and almond was also included in the list of priority allergens based on expert judgement. Table 1 shows the final recommendation from the Expert Committee.

Table 1. List of priority allergens currently in the GSLPF (FAO and WHO 2018), the new recommendation suggested by the FAO/WHO Expert Committee (FAO and WHO 2022b) and allergens listed in the Regulation (EU) no 1169/2011.

Priority allergens currently on the GSLPF list
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
Sulphite in concentrations ≥ 10 mg/kg
Recommendation based on the FAO/WHO Expert Committee 2022
Priority allergens
Cereals containing gluten (i.e. wheat and other *Triticum* species, rye and other *Secale* species, barley and other *Hordeum* species, and their hybridized strains)[a]
Crustacea
Eggs
Fish
Milk
Peanuts
Sesame
Specific tree nuts (almond, cashew, hazelnut, pecan, pistachio, walnut)
May be considered as priority allergens in individual countries
Mustard[b]
Lupin[b]
Tree nuts (Brazil nut, macadamia, pine nuts)[b]
Oats[b]
Celery[b]
Buckwheat[b]
Soybeans[c]
Watch list[d]
Pulses
Insects
Kiwi
List of allergens in Regulation (EU) no 1169/2011 on the provision of food information to consumers
Cereals containing gluten (wheat, rye, barley, oats, spelt, kamut or their hybridised strains) and products thereof[e]
Crustaceans and products thereof
Eggs and products thereof
Fish and products thereof[e]
Peanuts and products thereof
Soybeans and products thereof[e]
Milk and products thereof (including lactose)[e]
Nuts (almonds, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia or Queensland nuts) and products thereof[e]
Celery and products thereof
Mustard and products thereof
Sesame seeds and products thereof
Sulphur dioxide and sulphites at concentrations >10 mg/kg or >10 mg/litre in terms of the total SO_2
Lupin and products thereof
Molluscs and products thereof

[a]Barley and rye 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.
[b]Not listed as global priority allergens due to lack of data on prevalence, severity and/or potency, or due to regional consumption
[c]Not listed as global priority allergen due to a combination of low global prevalence, low allergenic potency and generally low severity
[d]Due to the increased consumption of plant-based foods, these foods were recommended to be evaluated when data on prevalence, severity and potency become available.
[e]With some exceptions, see Regulation (EU) no 1169/2011

Establishment of threshold levels in food of priority allergens (2nd meeting)

Study populations

Eliciting doses (ED) for 14 allergens were previously described and determined by Remington et al. (2020) and Houben et al. (2020) based on data from food challenges from 1750 individuals in the Food Allergy Research and Resource Program–Netherlands Organisation for Applied Scientific Research Food Allergen Threshold Database. A literature review identified an additional 47 studies containing quantitative food challenge data. Further, more data were also added from unpublished clinical datasets (~25 % of total data available) resulting in a total number of 3 400 study subjects. Supplementary Table 1 in Remington et al. (2020) provides the total number of data points for each of the allergenic foods along with the number of right- or left-censored subjects[5], geographic location, first mg protein dose in food challenge protocol and age groups when known. The number of subjects ranged from 1 306 for peanut to 25 for lupine. Since there were no published data on almond, no EDp value was proposed (Remington et al. 2020). The Expert Committee further found additional studies and the Allergen threshold database used by the Expert Committee to establish EDp-values contains data for more than 3 500 patients and 35 different allergens (FAO and WHO 2022c). However, additional data made no or little difference to the EDs presented in Houben et al. (2020) and Remington et al. (2020) (see below). Most study subjects were from the Netherlands followed by the US and France. Other European countries, including Nordic countries, were represented. Non-European countries were Australia, Brazil, Canada and Japan (Figure 1). Data from the Nordic countries are included in the determination of EDps for eggs, fish, hazelnut, milk, peanuts, shrimp (only Iceland) and wheat (Remington et al. 2020, suppl table 1). In chapter 6, The Expert Committee discusses the study populations (Remington et al. 2020, suppl. 1) and the quality and quantity of data and the potential for biases based on the number of study subjects and the age distribution and geographical dispersion of these (FAO and WHO 2022c):

- For **wheat** there was an adequate to good quantity of data (n = 99) for dose-distribution modelling and with high to adequate potential for biases. The latter due to the study population mainly composed of children (85, which is adequate considering this allergy decreases with age), but only from two Codex regions (Europe and Asia).
- For **fish** there was an adequate quantity of data (n = 82) for dose-distribution modelling and with an adequate potential for biases since there were no data available from Asia, Africa or South America where fish is commonly consumed. Furthermore, most data were from cod (64), followed by salmon (7), catfish (5) and mackerel (2).
- For **crustaceans** there was an adequate quantity of data (n = 75) but with a high potential for biases with all data related to different species of shrimp and that the study population only included two children. There were no left-censored data despite some of the studies started at

[5] Individuals were left-censored if they reacted with objective symptoms to the first challenge dose, while individuals were right-censored if they failed to respond with objective symptoms to the uppermost challenge dose but did have clear histories of allergic reactions upon consumption of the offending food

relatively high doses indicating a lower potency for shrimp compared to the other allergenic foods.

- For **sesame seeds** the original data-set of 40 persons from France and Netherlands (Remington et al. 2020) was up-dated with data from the United States to a final number of 67 DBPCFC, with and without inclusion of 179 open food challenge data from six studies (Turner et al. 2022b). Based on this larger data-set the quantity of data was considered good for dose-distribution modelling with adequate potential for biases; the full data-set including studies from seven countries in three Codex regions.
- For **hazelnuts** there was a good quantity of data (n = 411) with an adequate potential for biases. Although a good distribution of adults and children respectively all data were available from countries in Europe only and with a large proportion right-censored, probably due to birch-pollen related hazelnut-allergic individuals, shifting the dose-response curve to the right and leading to relatively large confidence intervals.
- For **cashew nuts** there was a good quantity of data (n = 245) but with high potential for biases. The latter was due to the population was composed of children exclusively (cashew allergy has a low resolution rate); all from the Netherlands. Furthermore 46 % of the dataset were either left (16/245) or right (112/245) censored. The EDps were transferred to the botanically related **pistachio nuts**.
- For **walnuts** there was an adequate amount of data (n = 74) but with high potential of biases since all data come from the Netherlands and more than half were issued from unpublished data. A pending study, also from Europe, would not alter these classifications. The EDps were transferred to the botanically related **pecan nuts**.
- For **hen's eggs** there was a good quantity of data (n = 431) with low potential for biases, although data originated from many countries they only included two regions (Europe and North America).
- For **cow's milk** there was a good quantity of data (n = 450) with low potential for biases. However, in a single dose-challenge study, consisting of 172 children, to validate the predicted ED05 of 2.4 mg twelve (7 %) experienced objective symptoms (Turner et al. 2021, see further below).
- For **peanuts** there was a good quantity of data (n = 1 306) with adequate potential for biases due to that the study population mostly was composed of children (1 079) in a proportion not representing the peanut allergic population.

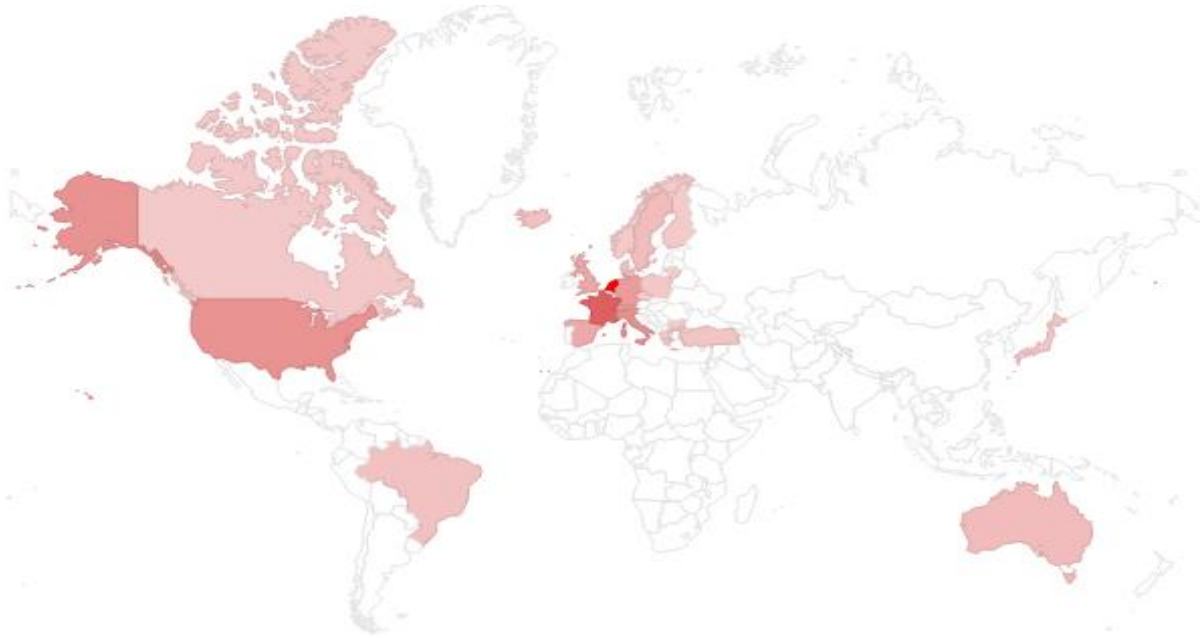

Figure 1. Heat-map over studies included in the Allergen threshold database used by the Expert Committee (FAO and WHO 2022c).

Calculation of eliciting doses

For the 14 dose-response distributions, only data from DBPCFCs were used, except in case of data from infants and very young children and for wheat. The data were collected and assessed in terms of discrete dose and cumulative dose datasets and expressed in mg of total protein of the allergen (Houben et al. 2020). Individual studies were combined per allergen and analysed with the Model Averaging approach developed by Wheeler et al. (2020). This approach combines five parametric survival distributions (Weibull distribution, Log-Gaussian (or Log-Normal), Log-Logistic, Generalized Pareto and Log-Laplace (or Log-Double-Exponential)) into a single model averaging outcome, which was used to determine population EDps on the basis of both discrete dosing and cumulative dosing. However, for most allergens the dose-response curve was best explained by the Weibull distribution (Supplement 2, Remington et al 2020). Houben et al. (2021) published tables providing ED01 to ED10 and ED15, ED20, ED25, and ED50 values for these 14 priority allergenic foods, including a 95 % confidence interval. All these EDp values were expressed as mg total protein of the allergenic food.

Most study subjects and data-points in the database were reported for peanut. The eliciting dose for a peanut-induced allergic reaction in 5 % of the population with peanut allergy (ED05) was previously estimated at 1.5 mg of peanut protein based on the population distribution of threshold doses (children and adults) from graded and blinded oral challenges of 750 patients with peanut allergy (Taylor et al. 2014). However, using a novel single dose challenge protocol, Hourihane et al (2017) documented that dosing peanut allergic individuals at the ED05 only resulted in mild symptoms. Further, the authors observed that only 2.3 % of the challenged individuals showed positive reactions at the ED05. In the updated population minimal eliciting dose distributions for use in risk assessment of 14 food allergens, the ED05 for peanut was set to 2.1 mg (95% CI: 1.2 - 4.6 mg) for the discrete dose dataset (Remington et al. 2020).

As described above (section Study population), the Expert Committee evaluated the quality and quantity of available data as well as the representativeness of studied populations and whether single-dose challenge studies were available for the verification of eliciting doses. For most allergens, the ED01 and ED05 reported by Remington et al. (2020) and Houben et al. (2020) were considered adequate with some considerations and the Expert Committee included more data for sesame and milk in its analyses leading to a later publication date for reference doses for sesame and milk.

In a single-dose study performed to validate the EDp of cow's milk, Turner et al. (2021) found a relatively larger proportion of participants to react with objective symptoms to suggested ED05 of milk (Remington et al. 2020; Houben et al. 2020) which raised concern. The Expert Committee noted the higher sensitivity in infants (< 3.5 years old) than in older children, but reasoned that the intake is easier to control in this group and that infants are relatively protected from severe reactions. Consequently, they considered that it is appropriate to base the reference dose on an ED05 derived from the whole population. An updated dose distribution analysis (Blom et al. 2022) including 697 data points did not significantly differ from the EDps reported in Houben et al. (2020) with ED05s of 2.4 mg and 3.2 mg milk protein respectively. A further review of the severity of reactions were undertaken prior to a decision of the RfD for milk (FAO and WHO 2022c).

An updated dose-distribution modelling for sesame was also performed including three different sets of data. Neither the ED01 nor the ED05 in Houben et al. (2020) did significantly change due to the inclusion of these data-sets although a slight shift to the left (lower ED05) was calculated, 2.4 mg compared to 2.7 for the discrete dose data-set (Turner et al. 2022b), which did not alter the suggested RfD (FAO and WHO 2022c, see further below).

Walnut and pecan are closely related botanically and the allergenic proteins have a high sequence similarity. Based on comparative studies the application of walnut EDps to pecan could be overly precautionary but it should be noted that a significantly larger number of patients reacted with severe symptoms to pecan compared to walnut (Goldberg et al. 2021). Similarly, pistachio is related to cashew and the EDps were assumed to be transferable. As mentioned above there are no data on almonds. Furthermore, almonds are not botanically related to any of the other tree-nuts and no EDp value can be proposed (FAO and WHO 2022c).

Determination of reference doses

The Expert Committee discussed and agreed on the safety objective described as "*to minimise, to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response, as defined by dose distribution modelling of minimum eliciting doses (MEDs) and supported by data regarding severity of symptoms in the likely range of envisioned Reference Doses (RfD)*" (FAO and WHO 2021b).

The Expert Committee discussed potential data sources and decided that the data reported in the publications of Remington, et al., (2020) and Houben, et al., (2020) were the most comprehensive and best source available. Further, dose-distribution analysis methodology was also well-described (see above). Hence, EDps reported by Remington et al. (2020) and Houben et al. (2020) formed the basis for the Expert Committee (FAO and WHO 2021b).

Characterisation of risk is the product of the number of affected people and the severity of these. The first part is covered by the prevalence and dose-distribution modelling, whereas the second element, severity, is an evaluation of the likely health impact. In Chapter 7.1, the Expert Committee discusses

the basic principles for the detailed hazard characterization at potential RfDs (FAO and WHO 2021c). They conclude that severity is a complex construct dependent on several factors and that, at a population level, dose appears to have a very limited role in determining severity of allergic reactions. Given these uncertainties, the experts concluded that the characterization of hazard must rely on actual data rather than on modelling approaches. Furthermore, the Expert Committee agreed to use "anaphylaxis" as the definition of severity for hazard characterization. However, "anaphylaxis" is not a single entity in terms of severity and the Expert Committee refers to the publication by Turner et al. (2022a) that suggests that at least 80 % of the anaphylaxes at ED05 of peanut exposure resolve spontaneously without treatment and that the remainder usually respond to a single dose of adrenaline. Furthermore, Turner et al. (2022a) predicts < 1 event of severe anaphylaxis per 60 000 exposures to ED05 and < 1 event of fatal anaphylaxis per 1 million exposures to ED05. There are currently no reports in the literature of fatal reactions to this level of exposure, for any allergenic food.

Based on the reasoning above, the Expert Committee reviewed two sources of data on severity: 1) evidence of anaphylactic reactions in clinical data at defined doses and 2) data on objective symptoms associated with reactions up to and including the ED01, ED05 and ED10 reported by Remington, et al. (2020) and Houben, et al. (2020). These data were collected from the review by Basseggio Conrado et al. (2021) (FAO and WHO 2021b).

The approach adopted by the Expert Committee was to assess the likelihood of allergic symptoms (including anaphylaxis) to *peanut* at low-doses of exposure (up to approximately the ED05 95 percent confidence interval upper bound, UCL, included in Table 2) and then evaluate whether allergic reactions to peanut can be considered a "worst-case" scenario by assessing the available evidence for other priority allergens. The conclusion was that reported symptoms up to ED05 (UCL) fell into a mild or moderate category for all considered allergens for which data could be provided (FAO and WHO 2022c). Although clinical data from controlled challenges indicated that up to 5 % of reactions at both ED01 and ED05 could be classified as anaphylaxis, the Expert Committee concluded that none was severe (i.e. life-threating or refractory) based on the World Allergy Organisation (WAO) definition (Cardona et al. 2020)[6]. Therefore, the Expert Committee agreed that, for all priority allergens, the safety objective would be met by a RfD at ED05. To make the application easier, the Expert Committee simplified its recommendations by rounding the ED05 values down to one significant figure on the basis of the size of the confidence interval and the quality and quantity of data. Some exceptions were made due to the risk of bias in the data-set (cashew, walnut), or if there was an uncertainty about the true ED05 value due to limited number of species tested within a food group, *e.g.* fish (mainly cod tested) and crustaceans (mainly shrimp tested). The RfD for these were rounded down further than for the other foods (FAO and WHO 2022c) (Table 2)[7]. The suggested RfDs have shown to be protective in single dose challenge studies for peanut (Patel et al. 2021, Turner et al. 2022a) and milk (Turner et al. 2021) and through general experience with the Voluntary Incidental Trace Allergen Labelling (VITAL) Program[8] (FAO and WHO 2021b). The Expert Committee

[6] The WAO grading of allergic reactions includes five grades, where grade 1 and 2 are non-anaphylactic and grade 3-5 are anaphylactic. How this grading relates to the terms "mild", moderate" and "severe" reactions/symptoms used by the Expert Committee is unclear

[7] However, for cashew and walnut, the ED05 was rounded up to 1.0 mg from 0.8 mg (Table 2). In an unpublished study on walnut, five of 41 (12 %) children reacted to the first dose of 1.05 mg protein (FAO and WHO 2022c).

[8] The Voluntary Incidental Allergen Labelling Program of The Allergen Bureau of Australia & New Zealand is a standardised allergen risk assessment process for food industry (VITAL® Voluntary Incidental Trace Allergen Labelling (allergenbureau.net))

recommends the RfD to be used for risk management of unintended allergen presence in foods during an evaluation period of at least five years.

Table 2. Reference doses (RfD) suggested by the FAO/WHO Expert Committee (FAO and WHO 2021b, 2022a) and ED05 including 95 % confidence interval (Houben et al. 2020)

Allergen	RfD	ED05 (95 % CI)
	mg total protein from the allergenic source	
Tree nuts[a] (almond, cashew, pecan, pistachio, walnut)	1.0	0.8 (0.1 – 8.9)[b] 0.8 (0.2 – 5.0)[c]
Peanuts	2.0	2.1 (1.2 – 4.6)
Eggs	2.0	2.3 (1.2 – 4.7)
Milk	2.0	2.4 (1.3 – 5.0)
Sesame	2.0	2.7 (0.4 – 34)
Hazelnut	3.0	3.5 (1.3 – 12)
Wheat	5.0	6.1 (2.6 – 16)
Fish	5.0	12 (4.5 – 44)
Shrimp	200	280 (69 – 880)

[a] Tree nuts apart from hazelnut which has a higher recommended reference dose (3.0 mg total protein); [b] data for walnut; [c] data for cashew

Hazard identification and characterisation

Prevalence of food allergies

The Expert Committee suggested reference doses for milk, eggs, fish, shrimp/crustacean, wheat, peanuts, sesame, almond, cashew, hazelnut, pecan, pistachio and walnut (Table 2). The prevalence of allergy to these foods was assessed and classified and the results of this review are presented in the meeting report (FAO and WHO 2022b). Grade 1 and Grade 2 evidence (see section "Prevalence" in the Introduction) was used in the classification of prevalence. Below and in Table 3, we summarize European prevalence data from the FAO/WHO meeting report for foods with suggested reference doses. Soybean is also discussed and included in Table 3.

The prevalence of **cow's milk allergy** was classified from low in adults to high in infants and young children and the Expert Committee concluded that most infants outgrow their allergy as they reach school age (FAO and WHO 2022b). Meta-analyses based on grade 1 and grade 2 European data showed an overall prevalence of 0.6 % and 1.6 %, respectively (Nwaru et al. 2014). Grade 1 evidence from studies of European infants (EuroPrevall cohort, from birth to 2 yrs) showed an adjusted prevalence of 0.7 % (Schoemaker et al. 2015). There were no grade 1 data on older children and adults, but grade 2 data from school-aged children (EuroPrevall study) showed a prevalence of probable milk allergy ranging from 0 % to 1.7 % in different countries (Lyons et al. 2020). The Expert Committee concluded that the prevalence in studies of adults was considerably lower. There were no grade 1 data on adults, but grade 2 data showed that prevalence ranged from 0.0 % to 0.2 % in European adults (EuroPrevall study) (FAO and WHO 2022b).

Similar to cow's milk allergy, **hen's egg allergy** is most common in infants who often outgrow their allergy before school-age. Thus, the Expert Committee classified the prevalence as high in infants and low in adults (FAO and WHO 2022b). A meta-analysis with grade 1 and grade 2 data from European studies showed an overall prevalence of 0.2 % and 1.0, respectively (Nwaru et al. 2014). In infants from birth up to 2 years of age (EuroPrevall study, grade 1 data), Xepapadaki et al. (2016) reported an overall prevalence of 0.8 %, ranging from 0.1 % to 2.0 %. Among European school-aged children, grade 1 data (EuroPrevall-study) showed a prevalence of 0.05 %, while grade 2 data resulted in a prevalence between 0.0 % and 0.9 % depending on country. There were no grade 1 data on adults, but grade 2 data from the EuroPrevall-study showed a prevalence of 0.3 % in Poland and 0.0 % in the Netherlands (FAO and WHO 2022b).

Prevalence of **fish allergy** was classified as low in all ages although the prevalence was higher in adults than in school-aged children and infants (FAO and WHO 2022b). Grade 1 and grade 2 evidence from the European meta-analysis by Nwaru et al. (2014) showed an overall prevalence of 0.1 % and 0.0 %, respectively. In infants in the UK, the prevalence was 0.1 % (grade 1 data) and in European children the prevalence varied between 0.0 % and 0.3 % (FAO and WHO 2022b). Two systematic reviews of European data on adults (grade 1) showed a prevalence of < 0.3 and 0.15 %, respectively. Grade 2 data from studies in children (EuroPrevall-study) showed rates between 0.0 % and 0.5 % and similar data from adults indicated rates from 0.0 % up to 0.4 % (FAO and WHO 2022b; Lyons et al. 2019, 2020).

Overall prevalence of **crustacean shell fish allergy** was classified as mixed in adults and children based on grade 1 and 2 data and prevalence in infants was classified as low (FAO and WHO 2022b). The assessment was mainly based on data related to shrimp, with some data on crab from China and Thailand. Grade 1 evidence from the European meta-analysis by Nwaru et al. (2014) showed an overall prevalence of 0.1 % in all ages and a prevalence of 0.1 % in infants. Grade 1 data from a Danish study showed a prevalence of < 0.1 % in infants, < 0.1 % in children and ~0.3 % in adults. In the EuroPrevall-study follow-up at school-age, the prevalence was 0.1 % (grade 1 data). Grade 2 data from the EuroPrevall-study showed prevalence between 0.0 % and 0.7 % in children and between 0.0 % and 1.5 % in adults (Lyons et al 2019, 2020).

The overall prevalence of **IgE-mediated allergy to wheat** was classified as low in all age groups (FAO and WHO 2022b). The European meta-analysis by Nwaru et al. (2014) found an overall prevalence of 0.1 % (grade 1) and 0.3 % (grade 2). Grade 1 data in infants and children indicated a prevalence between 0.0 and 0.5 % while grade 2 data (EuroPrevall study) vary between 0.0 and 0.2 % in children and between 0.0 and 0.4 % in adults (FAO and WHO 2022b).

The overall prevalence of **peanut allergy** was classified as high in infants and children and low in adults (FAO and WHO 2022b). The meta-analysis from 2014 indicates a prevalence of 0.2 % based on food-challenge (grade 1) and 1.6 % based on grade 2 data (Nwaru et al. 2014). Based on grade 1 and grade 2 data in school-aged children (EuroPrevall study), Grabenhenrich et al. (2020) reported a rate of 0.14 and 2.8 %, respectively. In addition, grade 2 data from the EuroPrevall study showed a prevalence between 0.0 and 0.9 % in school-aged children and between 0.0 % and 0.5 % in adults (FAO and WHO 2022b). There were studies from Australia and Canada (grade 1) showing higher rates in infants and children than the European data.

The Expert Committee classified the prevalence of allergy to **sesame** as low in infants and very low in children and adults (FAO and WHO 2022b). No European data was available, but grade 1 data from Israel and Australia indicated a prevalence between 0.4 and 0.7 % in infants, 0.1 % in school-aged children and 0.09 % in adults (FAO and WHO 2022b). Grade 2 data indicated even lower prevalence.

Data on the prevalence of **almond allergy** were sparse and only available for school-aged children (FAO and WHO 2022b). However, the prevalence was classified as very low based on rates between 0.0 (Swedish/Icelandic data, grade 1) and 0.3 % (Australian data, grade 1) in this age group. Grade 2 data showed a prevalence of 0.2 % in children in the UK. (FAO and WHO 2022b).

Based on a limited number of studies of **cashew nut allergy**, showing very divergent rates, the prevalence was classified as mixed (FAO and WHO 2022b). There was only one European grade 1 study available showing a prevalence of 0.01 % in school-aged children. On the other hand, Australian studies in children indicated rates from 0.4 to 2.7 %. Grade 2 studies in the UK showed a prevalence of 0.1 % in infants and 0.2 % in school-aged children (FAO and WHO 2022b). The Expert Committee concluded that there is data from a study by Brough et al. (2020) indicating that cashew-nut allergy is closely related to pistachio allergy. In that study, 83 % of the participating children allergic to cashew were also allergic to pistachio and 97 % of the children with pistachio allergy were allergic to cashew.

The prevalence of **pistachio allergy** was classified as mixed based on a very limited number of studies (FAO and WHO 2022b). Grade 1 data from studies in Australia and Turkey showed a prevalence of 0.08 % and 0.1 % in school-aged children, respectively. Grade 2 data (Australia) showed a rate of 0.9 % in school-aged children. It was not possible to draw conclusions about prevalence in different

parts of the world or in different age groups. As mentioned above, pistachio nut allergy was highly related to cashew nut allergy.

The prevalence of **hazelnut allergy** was classified as mixed in children and adults and as very low in infants (FAO and WHO 2022b). Grade 1 prevalence data was mainly from Australia and South Africa, but a European study (EuroPrevall) indicated a prevalence of 0.3 % in school-aged children. Prevalence of probable allergy (grade 2) were 0.1 % to 2.2 % in European school-aged children and 0.1 % to 2.6 % in European adults (FAO and WHO 2022b, Lyons et al. 2019). The Expert Committee also noted that the pattern of allergy may be linked to birch pollen and that hazelnut allergy exists in a milder form associated with birch pollen and in a form that is associated with more severe reactions due to sensitization to other proteins (FAO and WHO 2022b). In the study of coexistent nut allergy by Brough et al. (2020), hazelnut allergy was strongest correlated to allergy to macadamia nut, pecan and walnut.

Based on a very limited amount of data, the Expert Committee classified prevalence of **pecan nut allergy** as very low although it was not possible to assess whether the rate of allergy changes with age or geography (FAO and WHO 2022b). All available prevalence data was from Australia and showed a prevalence of 0.02 % in infants and 0.04 % in school-aged children (grade 1). Based on grade 2 data, the prevalence in children was 0.2 % (FAO and WHO 2022b). Allergy to pecan and walnut was highly correlated in the study by Brough et al. (2020) where almost all children (97 %) with pecan allergy were allergic to walnut but only 75 % of children with walnut allergy were allergic to pecan. The Expert Committee also concluded that the prevalence of pecan allergy was lower than that of walnut and its distribution may be related to consumption patterns (FAO and WHO 2022b).

Prevalence of **walnut allergy** was overall classified as low (FAO and WHO 2022b). Grade 1 data indicated a prevalence of 0.02 % in European school-aged children (EuroPrevall study) and 0.04 % in 13-year-olds in Turkey. An Australian study in infants showed a prevalence of 0.1 % (Peters et al. 2017). Grade 2 data from the EuroPrevall study resulted in rates between 0.0 and 0.6 % in school-aged children and between 0.05 and 0.7 % in adults (FAO and WHO 2022b, Lyons et al. 2019, 2020). As mentioned above, allergy to walnut and pecan have been shown to be highly related.

Table 3. Summary of prevalence data (European studies unless otherwise stated) for suggested priority allergens and soybean. Based on prevalence data compiled by and classification suggested by the FAO/WHO Expert Committee (FAO and WHO 2022b). Bold percentages are used in Table 4 and represent the lowest and highest prevalence in infants/children and adults, respectively.

Allergen	**Overall (global) prevalence classification[a]**	**Prevalence data from studies of (mainly) European populations [95% confidence intervals in brackets]**	
		Grade 1 data[b]	**Grade 2 data[c]**
Cow's milk	High (overall) High (infants) Low (children) Very low (adults)	0.6% **[**0.5-0.8**]** (meta-analysis) 0.7% [0.6-1.0] (infants)	1.6% [1.2-1.9] (meta-analysis) **0%** [0.0-0.5] to **1.7%** [0.7-3.2] (school-aged children) **0%** [0.0-0.2] to **0.2%** [0.0-1.0] (adults)
Hen's eggs	High (overall) High (infants) Mixed (children) Low (adults)	0.2% [0.2-0.3] (meta-analysis) 0.8% [0.7-1.0] (infants), range: 0.1% [0-0.6] to **2.0%** [1.1-3.1] 0.05% (school-aged children)	1.0 [0.8-1.3] (meta-analysis) **0%** [0.0-0.5] to 0.9% [0.1-2.5] (school-aged children) **0%** [0.0-0.2] and **0.3%** [0.01-1.1] (adults)
Fish	Low (overall) Low (infants) Low (children) Low (adults)	0.1% [0.02-0.2] (meta-analysis) 0.1% [0.0-0.6] (infants) 0% [0.0-0.1] to 0.3% [0.0-2.0] (children) <0.3% [0.0-~1] (adults, systematic review) 0.15% [0.0-0.4] (adults, meta-analysis)	0% [0.0-0.1] (meta-analysis) 0% [0.0-0.4] to 0.5% [0.02-1.9] (children) 0% [0.0-0.3] to 0.4% [0.01-1.5] (adults)
Crustacean	Mixed (overall) Low (infants)	0.1% [0.06-0.3] (meta-analysis) 0.1% [0.0-0.3] (infants, meta-analysis) <0.1% [0.0-4%] (infants) <0.1% [0.0-~0.1] (children) 0.1% (school-aged children) ~0.3% [0.1-1] (adults)	0% [0.0-0.4] to 0.7% [0.06-2.2] (children) 0% [0.0-1.8] to 1.5 [0.4-3.3] (adults)
Wheat[d]	Low (overall) Low (infants) Low (children) Low (adults)	0.1% [0.01-0.2] (meta-analysis) **0%** (infants) 0.05-**0.5%** (school-aged children)	0.3% [0.02-0.6] (meta-analysis) 0.2% (infants) **0%** [0.0-0.4] to 0.2% [0.0-1.0] (children) **0.0%** [0.0-0.4] to **0.4%** [0.02-1.3] (adults)
Peanut	High (overall) High (infants) High (children) Low (adults)	0.2% [0.2-0.3] (meta-analysis) 0.14% [0-0.4] (school-aged children)	1.6% [1.2-1.9] (meta-analysis) **2.8%** (school-aged children) **0%** [0.0-0.9] and 0.9% [0.1-2.5] (school-aged children) **0%** [0.0-0.3] and **0.5%** [0.05-1.5] (adults)
Sesame	Low (overall) Low (infants) Very low (children) Very low (adults)	No European data 0.7% (infants, Israel) 0.6% [0.5-0.9] (infants 1 year, Australia) 0.4% [0.3-0.6] (infants, 4 years, Australia) 0.1% (school-aged children, Australia) 0.09% (adults, Israel)	No European data 0.2% (infants, Israel) 0.03% [0.0-0.06] (school-aged children, Canada) 0.01% [0.0-0.02] (adults, Canada)

Allergen	Overall (global) prevalence classification[a]	Prevalence data from studies of (mainly) European populations [95% confidence intervals in brackets]	
		Grade 1 data[b]	Grade 2 data[c]
Almond	Very low (overall) Insufficient data (infants & adults)	**0%** (school-aged children in Sweden and Iceland) 0.0 to 0.3% [0.1-0.5] (school-aged children, Australia)	**0.2%** (school-aged children)
Cashew	Mixed (overall) Mixed (infants) Mixed (children) Mixed (adults)	1.1% (infants, Australia) **0.01%** (school-aged children) 0.4 and 2.7% [2.2-3.3] (school-aged children, Australia)	0.1% (infants) **0.2%** (school-aged children)
Pistachio	Mixed (overall) Insufficient data (infants) Mixed (children)	0.1% (school-aged children, Turkey) 0.08% (school-aged children, Australia)	0.9% (school-aged children, Australia)
Hazelnut	Mixed (overall) Very low (infants) Mixed (children) Mixed (adults)	0.3% (school-aged children)	**0.1%** [0.03-0.6] and **2.2%** [0.4-5.3] (school-aged children) **0.1%** [0.0-0.6] and **2.6%** [1.5-4.0] (adults)
Pecan	Very low (overall) Very low (infants) Very low (children) Insufficient data (adults)	No European data 0.02% (infants, Australia) 0.04% (school-aged children, Australia)	No European data 0.2% (school-aged children, Australia)
Walnut	Low (overall) Very low (infants) Low (children) Low (adults)	0.1% (infants, Australia) 0.02% (school-aged children) 0.04% (school-aged children)	**0.0%** [0.0-0.4] to **0.6%** [0.0-2.5] (school-aged children) **0.05%** [0.02-0.5] to **0.7%** [0.1-1.9] (adults)
Soybean	Low (overall) Low (infants) Low (children)	0.3% [0.1-0.4] (meta-analysis) **0.0%**-0.07% (infants, Iceland) **0.0%** (infants, Sweden) 0.4% [0.1-0.8] (infants, UK) **0.0-0.5%** (school-aged children) **0.0-0.1%** (adults, Denmark)	**0.0%** [0.0-0.5] to 0.3% [0.01-1.1] (school-aged children) **0.0%** [0.0-0.3] to **0.1%** [0.02-0.6] (adults)

[a]Classification: insufficient data, very low (<0.5% in one region only or <0.1% in all regions), low (<0.5% in all regions), mixed (>1% in one region and 0.5–1.0% in at least one other region), high (>1.0% in more than one region). A consensus was arrived at over an overall prevalence score (FAO and WHO 2022b).
[b]Confirmed allergy determined with "gold standard tools". For IgE-mediated allergy, this meant a clinical history of reaction to food, together with evidence of sensitization to that food (skin prick test and/or food allergen specific IgE) and a positive oral food challenge.
[c]Probable adverse reactions to a food with symptoms that were consistent with a particular immune-mediated adverse reaction to the food and evidence of a disease biomarker (such as skin prick test and/or food allergen specific IgE).
[d]IgE-mediated allergy

Soybean – prevalence and severe reactions

The Expert Committee recommended that soybean should be removed from the global list of priority allergenic foods for labelling purposes based upon: (i) the generally low (global) 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 globally (FAO and WHO 2022b). Although the eliciting dose for the most sensitive percentile (ED01) is estimated at 0.5 mg soybean protein, the ED05 (10 mg) is higher compared to the protein fractions of most other priority allergens, except crustacean, shellfish and shrimp (Houben et al. 2020). According to the publication of Baseggio Conrado et al. (2021), evidence of reports of anaphylactic reactions to soybean were very rare on a global basis. The Expert Committee therefore concluded that the 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. However; due to soybean's widespread use in food products, the Expert Committee recommend that it may be kept on a list of allergens for regional consideration (FAO and WHO 2022b).

In the evaluation from 2014, EFSA concluded that the prevalence of clinically confirmed soy allergy in unselected populations in Europe appears to be low, although available studies are scarce. EFSA referred to Swedish studies where a medical history was combined with sensitisation and the prevalence of soy allergy was zero in 18-month-olds (N = 328) (Kristjansson et al. 1999) and 1.6 % in 4-year-olds (N = 2563) (Östblom et al. 2007). In addition, EFSA referred to two Danish studies that assessed soy allergy using oral food challenges. Osterballe et al. (2005) found a zero prevalence in children (N = 898) and adults (N = 936) and Osterballe et al. (2009) found a prevalence of 0.1 % in young adults (N = 843).

The Expert Committee classified the overall prevalence of soy allergy as low (FAO and WHO 2022b) (Table 3) and also concluded that prevalence is higher in infants than in school-aged children. There was insufficient data to come to a firm conclusion on prevalence in adults. The assessment was based on for instance a meta-analysis by Nwaru et al. (2014), estimating the overall prevalence to be 0.3 % based on food challenge positivity (grade 1 data) in European populations. The Expert Committee concluded that this prevalence was almost exclusively due to a high rate in young infants and that infants generally outgrow their allergy at school age (Savage et al. 2010). There were insufficient data to compare the pooled estimates between age groups (Nwaru et al. 2014). In their review, the Expert Committee also refers to north European grade 1 data indicating rates between 0.0 and 0.4 % in infants, between 0.0 and 0.5 % in school-aged children and between 0.0 and 0.1 % in adults (Table 3). European data on probable allergy (grade 2 data) indicated rates between 0.0 and 0.3 % in school-aged children and from 0.0 to 0.1 % in adults (Table 3) (FAO and WHO 2022b; Lyons et al. 2019, 2020).

Apart from the population allergic to soy, it is rather common with cross-reactivity to soy amongst peanut or birch pollen sensitised individuals, described in Livsmedelsverket (2021) and Cabanillas et al. (2018). Savage et al. (2010) identified a subset of patients with late-onset soy allergy whose symptoms started after tolerating soy on a regular basis in their diet, suggesting there are two soy allergy phenotypes, with the late-onset variety possibly related to either birch pollen cross-reactivity or persistent peanut allergy. According to Foucard et al. (1999), peanut and soybean were the most common causes of severe and even fatal reactions to foodstuff in Sweden in 1993-1996. Four fatalities were reported due to ingestion of foods containing soy in asthmatic patients severely allergic to peanut with no previously known allergy to soy (Foucard et al. 1999). However, the exposure doses in these

cases were uncertain and hidden peanut exposure as trigger of the reactions could not be ruled out (EFSA 2014). In 2005, Foucard et al. reported that the number of severe reactions to soy were fewer in 1997 - 2003 than in 1993 - 1996, probably due to different safety measures (Foucard et al. 2005). In the systematic review of anaphylaxis cases (data published January 2010 to November 2020) by Bassegio Conrado et al. (2021) one soy anaphylaxis fatality was recorded (from France, Poussel et al. 2019). The authors noted that soy was not a major cause of food anaphylaxis in any region and never to low (< 200 mg) doses (FAO and WHO 2022c).

The expected rate of anaphylaxis among allergic individuals after exposure to soy at ED05 is 0 per 1000 (95% CI 0 - 8) (Table 4) and the calculated/expected rate in the whole population is 0 (95% CI 0 - 4) per 100 000 infants/children and 0 (95% CI 0 - 1) per 100 000 adults (Table 4).

Consequences of suggested reference doses in sensitive populations

We have chosen to define sensitive populations as the individuals within a population allergic to a specific food allergen that will react with objective symptoms to a dose equal to ED05 for that food, *e.g.* the most sensitive 5 % to each allergen. Based on the overall prevalence (Table 3), the number of individuals at risk, in different age groups (where data is provided), can be estimated. Further, the severity of reactions to low doses was considered. Using peanuts as an example, 0.23 % (*i.e.* 4.5 % of the most sensitive 5 %) of the population allergic to peanuts are estimated to react with anaphylaxis, however with mild to moderate symptoms (Patel et al. 2021; Turner et al. 2022a). The detailed hazard characterisation made for the other allergens at ED05 (UCL) did not depart from these observations of peanut (FAO and WHO 2022c). The anaphylaxis rates from exposure to low doses of peanuts and other allergens are listed in Table 4. Many of them are around or slightly lower than for peanuts, however with larger confidence intervals due to less amount of data (study subjects/number of food challenges).

The rate of allergic individuals that are expected to react with anaphylaxis at ED05 are estimated to about 1 per 1000 for wheat, eggs and hazelnut and about 2 – 3 per 1000 for milk, peanuts, cashew and walnut (Table 4). Taking into account the prevalence of allergy to each food from European studies, the expected rate of anaphylaxis in the whole population at ED05 seems to be highest for peanuts in children (6 per 100 000), followed by milk (infants/children), hazelnut (children/adults), eggs (infants/children) and walnut (children/adults) (Table 4). The expected rates of anaphylaxis at exposure to ED05 (from Turner et al. 2022a) have very wide confidence intervals, and this adds uncertainties to the estimates, especially for wheat and egg. In addition, the prevalence estimates vary greatly between studies and often includes a zero prevalence. Accordingly, the expected rates of anaphylaxis in the whole population may be overestimated because the highest prevalence in European studies have been used in the calculations (Table 4). There were no data on anaphylaxis rates at low doses for pecan and pistachio nuts, sesame, almond, fish and crustaceans/shrimp. These allergens are thus not included in Table 4. However, Table 4 covers the allergens that are most common in unexpected reactions reported to the Swedish Food Agency allergy register (see below) and allergens that are most common as initiator of RASFF notifications in the category “allergen” (Table 7).

Table 4. Expected rates of objective symptoms and anaphylaxis at ED05 among allergic individuals and in the whole population. Calculations are based on European prevalence data from Table 3. Included allergens are those with both a suggested Reference dose (FAO and WHO, 2022a) and data on anaphylaxis rate at ED05 (Turner et al. 2022a). Soy is also included.

Allergen	Prevalence of allergy[a]	Expected rate of objective symptoms to exposure at ED05 (whole population)[b]	Expected rate of anaphylaxis to exposure at ED05 (among individuals reacting to ED05 with objective symptoms) (95% confidence interval)[c]	Expected rate of anaphylaxis to exposure at ED05 (among allergic individuals) (95% confidence interval)	Expected rate of anaphylaxis to exposure at ED05 (whole population) (95% confidence interval)[d]
Milk	0-1.7% (infants/children) 0-0.2% (adults)	0-9 per 10 000 infants/children 0-1 per 10 000 adults	4.9% (2.1-11)	2.5 (1.1-5.5) per 1000	4 (2-9) per 100 000 infants/children 0.5 (0.2-1) per 100 000 adults
Wheat	0-0.5% (infants/children) 0-0.4% (adults)	0-3 per 10 000 infants/children 0-2 per 10 000 adults	2.2% (0.02-75)	1.1 (0-38) per 1000	0.6 (0-19) per 100 000 infants/children 0.4 (0-15) per 100 000 adults
Eggs	0-2.0% (infants/children) 0-0.3% (adults)	0-10 per 10 000 infants/children 0-2 per 10 000 adults	1.5% (0.02-55)	0.8 (0-28) per 1000	2 (0-55) per 100 000 infants/children 0.2 (0-8) per 100 000 adults
Peanuts	0-2.8% (children) 0-0.5% (adults)	0-14 per 10 000 children 0-3 per 10 000 adults	4.5% (1.9-10)	2.3 (1.0-5.1) per 1000	6 (3-14) per 100 000 children 1 (0.5-3) per 100 000 adults
Hazelnut	0.1-2.2% (children) 0.1-2.6% (adults)	0.5-11 per 10 000 children 0.5-13 per 10 000 adults	2.5% (0.3-16)	1.3 (0.2-7.9) per 1000	3 (0.3-17) per 100 000 children 3 (0.4-21) per 100 000 adults
Cashew	0.01-0.2% (infants/children)[e]	0.1-1 per 10 000 infants/children	4.9% (2.2-10.5)	2.5 (1.1-5.3) per 1000	0.5 (0.2-1) per 100 000 children
Walnut	0-0.6% (children) 0.05-0.7% (adults)	0-3 per 10 000 children 0.3-4 per 10 000 adults	5.3% (2.0-13)	2.7 (1.0-6.5) per 1000	2 (0.6-4) per 100 000 children 2 (0.8-4) per 100 000 adults
Soy	0-0.5% (infants/children) 0-0.1% (adults)	0-3 per 10 000 infants/children 0-0.5 per 10 000 adults	0% (0-16.8)	0 (0-8.4) per 1000	0 (0-4) per 100 000 infants/children 0 (0-1) per 100 000 adults

[a]Prevalence is derived from Table 3. The highest and lowest observed prevalence (in European studies included in the evaluation by the Expert Committee (FAO and WHO. 2022b)) are selected for this table and used for the calculations of expected rates in the whole population. Infants/children and adults separately if possible.
[b]Based on prevalence interval in column "Prevalence of allergy" and assuming that 5% of allergic individuals react with objective symptoms to exposure at ED05
[c]Adapted from Turner et al. 2022a.
[d]Assuming the highest prevalence from the column "Prevalence of allergy" and using the confidence intervals of the expected rates of anaphylaxis to exposure at ED05.
[e]Based on very limited data.

Reported severe reactions in Sweden

Altogether 69 unexpected reactions to milk (42), eggs (17), hazelnut (3) or peanuts (7) were reported together with analyses of the suspected food to the Swedish Food Agency allergy register between 2003 and 2018. Severe reactions (grade 2 and grade 3 anaphylaxis, see section "Treatment" below) have mainly been elicited by high exposures; 110 mg egg protein, 770 mg peanut protein (Wilhemsson 2019) and 390 mg cow's milk protein (Eriksson 2019). However, anaphylaxis (grade 1) after low exposures (≤ RfD) have occurred to egg (four times) peanut (twice) and milk (once). Other reported symptoms after exposure to low doses of milk included abdominal pain, itchiness in throat and mouth, malaise and shortness of breath (Eriksson 2019). There are uncertainties around these data relating to estimated doses, *e.g.* measurement uncertainty as well as the fact that the allergen could have been un-homogenously distributed in the contaminated batch. This means that the analysed food can contain a higher or a lower concentration than the portion eaten (Livsmedelsverket 2022). Further the serving sizes were based on the medical journal report which not always were accurate and in some cases serving sizes based on food consumption data were used instead (Eriksson 2019; Wilhemsson 2019).

Treatment

The only way to avoid allergic reactions in individuals with food allergy is strict avoidance of trigger foods. Symptoms of an allergic reaction vary from mild to severe and can involve one or several organs such as the skin, mouth, stomach, airways and heart.

Mild to moderate allergic reactions in patients who are not at risk of anaphylaxis are treated with non-drowsy antihistamines and possibly with glucocorticoids (cortisone). Antihistamines have an effect on itching, urticaria and allergic rhinitis within 30 to 60 minutes. The effect of cortisone comes after a couple of hours, and the purpose of the medication is to block late effects of the allergic reaction. (SFFA 2015).

For long-term treatment, induction of tolerance development and desensitization by oral immunotherapy (OIT) has become an available option under specialist supervision in specialist care with standardised protocols and products approved by the U.S. Food and Drug Administration (FDA) and the European Medicines Agency (EMA). Peanut, egg and milk OIT to increase the amount of allergen tolerated while in therapy is now recommended for children in an updated food allergy management guideline developed by the Global Allergy and Asthma European Network (GA^2LEN) (Muraro et al. 2022a).

Anaphylaxis is the most severe clinical presentation of an allergic reaction. It is an acute, severe, systemic, hypersensitivity reaction that is potentially fatal. The reaction is often sudden and usually unanticipated, and it involves more than one organ system (Gülen and Wickman 2016). The reaction always includes an objective respiratory and/or cardiovascular effect and/or severe generalized symptoms (SFFA 2015). Symptoms from the skin, mucous membranes, gastrointestinal tract, urogenital system and central nervous system are also common. Symptom onset varies widely from within seconds to a few hours, but usually occurs within 30 minutes of exposure to the trigger (Gülen and Wickman 2016). Generally, the risk of a severe reaction is higher if the onset is fast (SFFA 2015).

The Swedish association for allergology (SFFA, Svenska föreningen för allergologi) has graded anaphylactic reactions in grade 1, 2 and 3 according to severity of generalized symptoms and

symptoms from the airways, cardiovascular system, and gastrointestinal tract. Cardiovascular effects (e.g. hypotension, bradycardia, arrhythmia, heart arrest) are characteristic of a grade 3 anaphylaxis. (SFFA 2015).

Cofactors that can increase the risk of or aggravate an anaphylactic reaction in some individuals are e.g. physical exercise, stress, sleep deprivation, infection, medications (for example non-steroidal anti-inflammatory drugs) and alcohol intake (Cardona et al. 2020; FAO & WHO 2022c; Muraro et al. 2022b). In exercise-induced food-related anaphylactic reactions, the symptoms may start during physical activity up to 4 hours after ingestion of the trigger food (SFFA 2015).

Although fatal and near-fatal reactions are rare, all anaphylaxis reactions must be appropriately treated to reduce risk of death (Cardona et al. 2020; Gülen and Wickman 2016). Early diagnosis and prompt initiation of treatment is important and the diagnosis should be established only when the diagnostic criteria are met. Any delay in the recognition of the initial signs and symptoms can result in a fatal outcome, because of either airway obstruction or circulatory collapse (Gülen and Wickman 2016).

Epinephrine (adrenaline) is the most important medication for anaphylaxis, and should be injected intramuscularly in the mid-anterolateral aspect of the thigh as early as possible after diagnosis (SFFA 2015). Patients at risk of anaphylaxis (i.e. patients who have experienced previous episodes of anaphylaxis) are prescribed an auto-injector of adrenaline (a so called “adrenalinpenna” in Swedish) to use in case of allergic reactions. It is important that the patients (or the guardians of young children) are trained in how and when to use the adrenaline auto-injector. After injection of adrenaline, the patient should urgently seek medical care and avoid physical activity. Two auto-injectors should always be available to avoid that the symptoms return before the patient reaches hospital.

At the hospital, a patient with an anaphylactic reaction get intramuscular injections of adrenaline every 5^{th} to 10^{th} minute. The patient is placed on the back with elevated lower extremities (or sitting with elevated legs if there is respiratory distress or vomiting). Fatality due to blood pressure drop can occur within seconds if the patient stands or sits suddenly (Cardona et al. 2020). Under certain circumstances, including no effects of repeated intramuscular injections, intravenous adrenaline may be given during careful ECG-monitoring (SFFA 2015). The treatment at hospital may also include bronchodilators (in patients with asthma), oxygen (in the case of hypoxia) and intravenous fluids. Antihistamine and cortisone should be administered later in the treatment process. Depending on the severity of the anaphylaxis, it is recommended that the patient is observed for 4 to 12 hours. (SFFA 2015).

Poorly controlled asthma may be a risk factor for severe anaphylaxis, and it is important that patients with asthma have access to fast-acting bronchodilating medication. Prescription of non-drowsy antihistamines and cortisone is also recommended to patients with prescribed adrenaline auto-injectors. The scientific evidence for treatment with these medicines in anaphylaxis are however insufficient and adrenaline should always be used before antihistamine and cortisone. (SFFA 2015)

Food allergen analysis

The Expert Committee observed that recommended RfDs can be implemented and monitored to some degree with current analytical capabilities but that significant limitations in method performance still exist (FAO and WHO 2022c). Table 5 lists the limits of detection (LOD) and the limits of quantification (LOQ) for 13 allergens at the in-house laboratory at the Swedish Food Agency and a

company that is currently available for allergen analysis within Europe. The column to the right lists calculated action levels for foods assuming portion sizes of 100 g and 500 g, respectively, since the action level depends on portion size; the larger portion size for a certain food, the lower the action level. With the exception of tree-nuts, allergens can be detected by enzyme-linked immunosorbent assay (ELISA) in concentrations down to these action levels. However, tree-nuts were mainly contaminants in food products consumed in smaller servings (see section “Exposure assessment”) and concentrations down to the action level for 100 g portions can be quantified (Table 5). For pistachio, only analysis with PCR was listed. The LOQ of 20 DNA copies equals a concentration of 10-50 mg allergenic food per kg food product and whether quantification down to the action level is possible depends not only on this span but also on the protein content in the allergenic food. With a protein content of 20 % the LOQ will be between 2 and 10 mg protein per kg food.

However, the Expert Committee recommends the method performance criteria (LOQ) for a specific food should be 3-fold lower than the action level for that food in order to account for variability and to assure that the analytical result is truly at or below the action level. Based on this, the RfD can be implemented and monitored to some degree with current analytical capabilities but that a number of limitations still exist such as lack of appropriate methods for the identification and quantification of wheat and fish and for the quantification of crustacean shellfish (FAO and WHO 2022c). If three times LOQ for a certain food allergen analysis should be above the action level the Expert Committee recommends a higher action level, i.e. equal to 3*LOQ, while awaiting improved methods. The full range of ED values (Houben et al. 2020) can help to assess the risk associated with such a temporary higher action level (FAO and WHO 2022c).

Besides analyses with PCR and ELISA, there is a potential to screen food products for specific peptides of several allergens with liquid chromatography–mass spectrometry (LC/MS) in a single analysis. The application of LC/MS to allergen quantification is relatively new, and common practices such as quantification standards, are not well-established (Holzhauser et al. 2020).

The Expert Committee recommends the development of method performance criteria, as well as more extensive provision of accessible reference materials, for the priority allergens to address deficiencies in analytical methodology. Further, there is a need for better understanding of assay performance in different food matrices and greater transparency over assay-specific reagents, such as antibodies used in ELISA, which are critical to assay performance. Improvements were also called for in sampling for analysis and curation of samples from originator to laboratory (FAO and WHO 2021b). In order to facilitate result interpretation and comparison with a reference dose, the Expert Committee further recommended that expression of analytical results should be standardized as mg total protein of the allergenic food per kg food product analysed (FAO and WHO 2021b).

Table 5. Limit of detection (LOD) and limit of quantification (LOQ) for allergen analysis with ELISA at the Swedish Food Agency and a commercial laboratory company performing allergen analysis in Europe. The LOQ is expressed as mg total protein of the allergenic food per kilogram of food product unless otherwise stated. The right columns show suggested action levels for food consumed in 100 g and 500 g serving sizes based on the FAO and WHO (2021b) recommended reference doses.

Allergen (protein)	**Swedish Food Agency**		**Laboratory analysing food in Europe**	**Action levels in food [mg/kg] assuming portions of:**	
	LOD [mg/kg]	**LOQ [mg/kg]**	**LOQ [mg/kg]**	**100 g**	**500 g**
Peanut	NA	NA	0.078 20 DNA kop[c]	20	4
Hazelnut	0.26	0.38	0.5	30	6
Almond	0.39	0.58	0.53	10	2
Walnut	0.3	0.36	0.3	10	2
Milk	0.15 (1.6)[a]	0.63 (3.1)[a]	0.63 (3.1)[a]	20	4
Gluten	3	5	5		
Wheat	3.75	6.25	6.25	50	10[e]
Hydrolysed matrix (gluten)	8	10	Wheat, rye, barley (PCR): 20 DNA copies[c]		
Eggs, egg white protein	0,03	0.13			
Total egg protein	0,06	0.28	0.5	20	4
Fish	2	5[b]	20 DNA copies[c]	50	10
Sesame	NA		6 20 DNA copies[c]	20	4
Cashew nut	NA		0.36	10	2
Crustaceans (tropomyosin)	NA		0.02[d] 20 DNA copies[c]	2000[f]	400[f]
Soya	0.24	2.5	2.5 20 DNA copies[c]	NA	NA
Pistachio	NA		20 DNA copies[c]	10	2

[a] Depending on matrix, heated products having the higher LOQ; The method detects casein which is appropriate for most food, however not products containing whey, for example margarine and protein shakes [b] The limit of quantification differs between fish species, the example is for cod; [c] According to the lab, 20 DNA copies equals a concentration between 10-50 mg total allergen per kg, conversion to mg protein depends on the protein content of the food in question; [d] For tropomyosin there are different conversion factors for different food. These factors should be provided by the lab in the protocol; [e]note that this is lower than the 20 ppm as the concentration threshold for gluten-free products; [f] For shrimp. With a conversion factor of 15 000 (blue mussel which is a high factor) the detection limit is 300 mg/kg.

Exposure assessment

RASFF-notifications due to allergens

Created in 1979, RASFF enables information to be shared efficiently between its members (EU Member State national food safety authorities, Commission, EFSA, ESA, Norway, Liechtenstein, Iceland and Switzerland) and provides a round-the-clock service to ensure that urgent notifications are sent, received and responded to collectively and efficiently[9]. The first ever notification on allergen was made in 1984 by Germany and concerned the product category "confectionary", food "sneezing powder" and substance/finding "dangerous". The next allergen entry to the system was made in 1996 but it was not until this millennium the system really was used for allergen notifications. Today there are between 200 and 300 notifications made yearly (Figure 2).

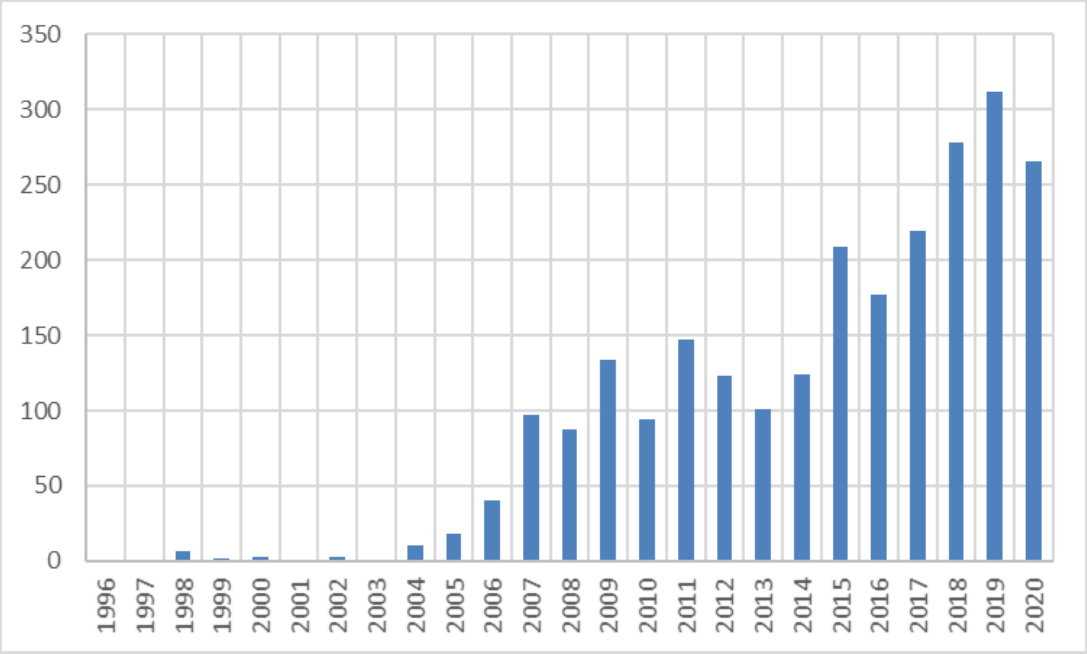

Figure 2. RASFF-notifications containing the hazard category "allergen" from 1996 to 2020.

All RASFF-notifications for the hazard category "allergen" between 1984 and 2020 are shown in Table 6, based on product category, and Table 7, based on the allergen found. Cereals and bakery products was the product category behind most of these notifications (421/2452). The most common substances, or undeclared allergens, were gluten and milk. Milk was further the finding that caused most allergen notifications (487/2452; Table 7) and the most common finding in prepared dishes and snacks as well as confectionary. Gluten and eggs are also quite often found in prepared dishes and snacks whereas undeclared peanuts and hazelnuts are common contaminants in confectionary and

[9] https://food.ec.europa.eu/safety/rasff-food-and-feed-safety-alerts_en

cocoa products such as chocolate (Table 6). Undeclared sulphite in concentrations above 10 mg/l was by far the most common finding in beverages and fruits and vegetables (Table 6). Further, sulphite was a common cause of notifications for the product category crustaceans and products thereof (Table 7). For meat and meat products, this was soy, followed by milk and gluten (Table 6).

There is uncertainty in the RASFF reporting related to potential duplications (several countries notifying the same product). Further, several allergens can be present in the same product, but potentially not reported separately. These factors can lead to relative over- as well as underestimations. Further, all allergen notifications are included in Tables 6 and 7. These were primarily due to mislabelling ("undeclared allergens") and secondly due to contamination ("traces of"). In conclusion, we consider RASFF notifications as an adequate data source that provides a good view of the most commonly found allergens as well as in which products. This is further in accordance with data reported from Sweden and the Netherlands, where chocolate/sweets, meat products (constituting part of a meal), ready-made meals, bread, cookies and cakes were the products that most commonly caused unexpected allergic reactions (Livsmedelsverket 2022).

Table 6. The most common product categories in which an allergen was the cause of a RASFF notification between 1984 and 2020 further divided into the most common finding/substance (allergen).

Product category	n	Substance/finding (n)
Cereals and bakery products	421	Gluten (97), milk (83), egg (33), peanut (33)
Prepared dishes and snacks	271	Milk (29), egg (26), gluten (18)
Confectionary	207	Milk (57), peanut (30), sulphite (29), gluten (12), hazelnut (12)
Fruits and vegetables	203	Sulphite (164)
Cocoa and cocoa preparations, coffee and tea	200	Milk (101), hazelnut (25), peanut (20)
Soups, broths, sauces and condiments	194	Milk (29), egg (26), gluten (18)
Nuts, nut products and seeds	120	Peanut (36), milk (15)
Meat and meat products (other than poultry)	120	Soya (30), milk (21), gluten (20)
Dietetic foods, food supplements, fortified foods	117	Milk (30), gluten (16)
Other food product/mixed	116	Milk (23), sulphite (13), soya (12), gluten (11)
Other (beverages, herbs and spices, ices and desserts, poultry meat and poultry meat products, eggs and egg products, milk and milk products etc)	483	Sulphite (118), milk (71), egg (54), mustard (33), gluten (32), soya (30), celery (29)

Table 7. The most common substances/findings in the hazard category "allergen" initiating a RASFF notification between 1984 and 2020 (n = 2452) further divided into the most common product categories in which there was a finding.

Allergen	n	Product category (n)
Milk	487	Cocoa and cocoa preparations, coffee and tea (101), cereals and bakery products (83), confectionary (57), prepared dishes and snacks (50)
Sulphite	400	Fruits and vegetables (164), crustaceans and products thereof (82), confectionary (29), soups, broths, sauces and condiments (23)
Gluten	248	Cereals and bakery products (97), prepared dishes and snacks (31), meat and meat products (other than poultry) (20), soups, broths, sauces and condiments (18), dietetic foods, food supplements, fortified foods (16)
Soya	213	Cereals and bakery products (60), meat and meat products (30), prepared dishes and snacks (26), confectionary (20)
Egg	179	Fish and fish products (37), soups, broths, sauces and condiments (26), prepared dishes and snacks (22), other food products/mixed (14)
Peanut	165	Nuts, nut products and seeds (36), cereals and bakery products (33), confectionary (30), cocoa and cocoa preparations, coffee and tea (20)
Mustard	114	Soups, broths, sauces and condiments (31), prepared dishes and snacks (17), spices and herbs (17), meat and meat products (13)
Wheat	101	Prepared dishes and snacks (19), cereals and bakery products (19), confectionary (13), other products/mixed (8)
Celery	93	Prepared dishes and snacks (23), soups, broths, sauces and condiments (21), spices and herbs (18)
Almond	76	Cereals and bakery products (13), cocoa and cocoa preparations, coffee and tea (8), spices and herbs (8), nuts, nut products and seeds (8), confectionary (7), ices and desserts (6)
Other (nuts and seeds, seafood, lactose, lactoprotein etc)	388	Cereals and bakery products (67), prepared dishes and snacks (56), cocoa and cocoa preparations, coffee and tea (48), dietetic foods, food supplements, fortified foods (33), confectionary (32), nuts, nut products and seeds (28), soups, broths, sauces and condiments (24)

Reported food allergy reactions in Sweden

Based on data from the Swedish Food Agency allergy register, reactions to food allergen exposure have been reported in Sweden between 2003 and 2018; described in the hazard identification and characterisation. The food products causing the reactions for peanut and hazelnut (11 reports) were in most cases chocolate or bakery products (3 times each). Prepared dishes, snacks, ice cream and tahini are other examples of contaminated products or undeclared allergens (Eriksson 2019; Wilhemsson 2019). Eggs (17 reports) were most often present in meat products (6 times), prepared dishes (4 times) and bakery and fish products (twice each) (Wilhemsson 2019). For milk (42 reports), the most common cause was contamination of prepared dishes (15), bakery products (10) and chocolate (6) (Eriksson 2019).

Portion sizes of the most commonly contaminated product categories

The Expert Committee recommends national consumption data to be used in order to determine action levels for different foods based on the RfDs. For this purpose, it is recommended to use the 75th percentile (p75) of consumption. This is in accordance with the risk assessment guideline of the Swedish Food Agency which also includes a table with food consumption data for 35 different foods including p75 (Livsmedelsverket 2022). Based on the RASFF reporting, milk, eggs and peanuts were the allergens of highest concern. Further, wheat (gluten) and almond are included in the priority list and are common contaminants in food (Table 7). A filtration on products (*e.g.* finer resolution than product category) and the serving sizes of these are briefly described below.

Milk was most often found as a contamination or undeclared allergen in "Cocoa and cocoa preparations, coffee and tea". Almost all of these alerts were from different varieties of chocolate. In the product category "Cereals and bakery products" milk was most often found in bakery products (often containing chocolate). The largest serving size (p75) reported for these products in Swedish dietary surveys was 100 g (chocolate). Milk has also been reported several times as an undeclared allergen in prepared dishes and snacks; both in RASFF notifications and in the Swedish Food Agency allergen register. This food category can potentially lead to higher exposures (e.g. larger portion sizes), for example 500 g of lasagna (Livsmedelsverket 2022). In Table 5, calculated action levels at portion sizes of 100 g and 500 g are presented. These are based on the recommended RfD, however not including measurement uncertainty. This upper limit covers the reported 75th percentiles (p75) of portion sizes apart from pizza where the portion size (p75) was reported to be 600 g (Livsmedelsverket 2022) and therefore can be of importance when considering exposure to wheat and/or gluten in products incorrectly labelled as gluten free (*i.e.* containing >20 ppm gluten). The LOQ of gluten is low enough in order to detect concentrations down to the action level, although not with a three-fold margin as recommended by the Expert Committee (Table 5). It should be noted that the suggested action level for wheat due to findings of gluten in food with portion sizes above 200 g is lower than 20 ppm gluten. The suggested RfDs are neither intended nor appropriate to be used to define "allergen-free" labelling (FAO and WHO 2022c).

Eggs have been notified as an undeclared allergen in fish products such as gratin with serving sizes up to 500 g (p75). The second highest product category was soups and broths with potential serving sizes of up to 350 g (p75). For peanuts and tree nuts, traces are most commonly notified in nuts and seeds (p75 of 54 g), cereals such as breakfast muesli (p75 of 45 g) and chocolate (p75 of 100 g). The LOQ for ELISA analysis is below the corresponding action levels for all these product allergen combinations even with a three-fold margin to the LOQ (Table 5). For pistachio, only PCR analysis is listed in table 5 and the action level is likely to be close to the LOQ in food consumed in 100 g portions.

Risk characterisation

Answers to specific questions

1. *Describe the methods used to calculate reference doses/eliciting doses of food allergens and the suggested global reference doses.*

Answer: The FAO/WHO Expert Committee's reasoning behind priority allergens and recommended reference doses for these is described in the Introduction of this report. The evaluation was done in a structured way based on available evidence and updated criteria taking into account global data on prevalence, potency and severity to prioritise allergens (Table 1). For the eight priority allergens, the Expert Committee chose to recommend reference doses equal to the ED05 mainly based on the discrete data sets reported by Remington et al. (2020) and Houben et al. (2020), but rounded down to one significant figure depending on data availability and of the size of the confidence interval (FAO and WHO 2022c) (Table 2). The decision to use ED05, *e.g.* compared to ED01, was justified by the fact that the severity of reactions to doses in this range all fell into a mild or moderate category, most often (~80 %) resolving without treatment and the extreme rarity of fatal cases; none to low doses (< 5 mg). Further refinement would not lead to any significant public health benefit, but would introduce considerable burdens and limitations for monitoring and potential unintended consequences on the application of PAL or other risk management strategies (FAO and WHO 2022c). Using peanuts as a reference allergen due to its extensive published data relating to over 3000 DBPCFC, 0.23 % of the allergic population is estimated to react with anaphylaxis after exposure to the RfD. The corresponding fraction if using ED01 instead of ED05 as the basis for RfD would be 0.04 % (Patel et al. 2022; Turner et al. 2022a). The Expert Committee does not expect these figures to be higher for any other allergen (FAO and WHO 2022c), see further answer 3.

2. *Is the Northern European population represented in the data used for calculations of these reference doses/eliciting doses?*

Answer: The data used for calculations of eliciting doses are described in the section Study population. Most study subjects are from the Netherlands followed by the US and France. Other European countries including Nordic countries were represented. Non-European countries were Australia, Brazil, Canada and Japan whereas no data has been published from Africa (Figure 1). Data from the Nordic countries are included in the determination of EDs for egg, fish, hazelnut, milk, peanut, shrimp (only Iceland) and wheat (Remington et al. 2020, suppl table 1). In FAO and WHO (2022c), Chapter 6, the quality and quantity of available data as well as the representativeness of studied populations is extensively reviewed and whether single-dose challenge studies were available for the verification of eliciting doses. This was taken into consideration when setting RfDs for the allergens (FAO and WHO 2022c).

3. *Which consequences might the proposed reference doses provoke? How many consumers will not be protected and how severely ill can they become? Is there any treatment for consumers that suffer from acute allergic reactions?*

Answer: The proposed reference doses are based on ED05s, and the proportions of individuals (among allergic individuals and in the whole population) that are estimated to react with anaphylaxis to doses

at ED05 are presented in Table 4 in the section "Consequences of suggested reference doses in sensitive populations". As also described in this section, the rate of allergic individuals that are expected to react with anaphylaxis at ED05 are estimated to about 1 per 1000 for wheat, egg and hazelnut and about 2-3 per 1000 for milk, peanut, cashew and walnut (Table 4). Taking into account the prevalence of allergy to each food (European studies), the expected rate of anaphylaxis in the whole population at ED05 seems to be highest for peanut in children (6 per 100 000), followed by milk (infants/children), hazelnut (children/adults), egg (infants/children) and walnut (children/adults) (Table 4). The expected rates of anaphylaxis at exposure at ED05 (from Turner et al. 2022a) have very wide confidence intervals, and this adds uncertainties to the estimates, especially for wheat and egg. In addition, the prevalence estimates vary greatly between studies and often includes a zero prevalence. Accordingly, the expected rates of anaphylaxis in the whole population may be overestimated because the highest prevalence in European studies have been used in the calculations (Table 4). There were no data on anaphylaxis rates at low doses for pecan and pistachio nuts, sesame, almond, fish and crustaceans/shrimp. These allergens are thus not included in Table 4. However, Table 4 covers the allergens that are most common in unexpected reactions reported to the Swedish Food Agency allergy register and allergens that are most common as initiator of RASFF notifications in the category "allergen" (Table 7).

Treatment of allergic reactions is described in the section "Treatment". In brief, mild to moderate allergic reactions in patients who are not at risk of anaphylaxis are treated at home with non-drowsy antihistamines and possibly with glucocorticoids (cortisone). Anaphylactic reactions are mainly treated with epinephrine (adrenaline) injected intramuscularly in the thigh. The treatment can start at home with prescribed adrenaline auto-injectors and continues at the hospital.

4. Describe the food categories that most commonly are contaminated with food allergens.

Answer: Table 6 in the exposure assessment lists the most common product categories leading to a RASFF notification for the hazard category "allergen". The most common findings/substances (e.g. allergens) are listed in Table 7 in the same section of the report. Cereals and bakery products was the product category behind most of these notifications followed by prepared dishes and snacks. The most common substances, or undeclared allergens, in these product categories were gluten, milk and eggs.

The figures in Table 6 and 7 include all allergen notifications. However, most of these were due to "undeclared allergens" and mislabelling, secondly due to contamination ("traces of"). In the Swedish Food Agency allergy register, most of the reported incidences were caused by contamination rather than undeclared allergens. The product categories implicated were mainly the same as the ones that are most commonly associated with RASFF notifications, *e.g.* prepared dishes, bakery products and chocolate (see further in the section Exposure assessment). This is also in accordance with data reported from Sweden and the Netherlands, listing chocolate/sweets, meat products (constituting part of a meal), ready-made meals, bread, cookies and cakes as the products that most commonly have caused unexpected allergic reactions (Livsmedelsverket 2022).

5. *Is it possible, for European food businesses and control authorities, to analyse food allergens in concentrations that correspond to the reference doses?*

Answer: The detection and quantification limits of prioritised allergens are shown in Table 5. With contamination of products in food categories for which portion sizes are around 100 g, the action level for a finding will be 10 times the RfD. Table 5 also includes an action level for food eaten in portions of 500 g, *e.g.* equal to twice the recommended RfD. Apart from tree nuts, concentration down to action levels can be quantified. However, tree-nuts are rarely contaminants in food products eaten in larger portion sizes than 100 g. Measurement uncertainty has not been taken into account for these action levels, but the Expert Committee recommends the method performance criteria (LOQ) for a specific food should be 3-fold lower than the action level for that food in order to account for variability and to assure that the analytical result is truly at or below this action level. Based on this, the RfD can be implemented and monitored to some degree with current analytical capabilities but that a number of limitations still exist such as lack of appropriate methods for the identification and quantification of wheat and fish and for the quantification of crustacean shellfish. There is further limited availability of reference material and absence of reference methods, a need to improve the recovery of proteins from complex food matrices and validation of method performance in these complex matrices (FAO and WHO 2022c).N.B. the suggested RfDs should not be used for labelling "free from".

6. *Describe the prevalence of soy allergy in Europe. Also, describe whether severe allergic reactions have been shown to soy in Europe.*

Answer: The prevalence of soy allergy and reports of severe reactions to soya are described in the section "Soybean – prevalence and severe reactions" in the Hazard identification and characterisation. Briefly, the prevalence is estimated to approximately 0-0.5 % in infants/children (Table 4) with the expectation to be outgrown in a majority of the population and therefore be lower in adolescents and adults (0-0.1 %). However, apart from the population allergic to soy, it is rather common with cross-reactivity to soy amongst peanut or birch pollen sensitised individuals.

Serious incidents after exposure to soy were reported in Sweden during the 1990s in individuals with known peanut allergy (Foucard et al. 1999). However, in 2005, Foucard et al. reported fewer severe reactions to soy in the period 1997 - 2003 compared to 1993 - 1996, potentially due to different safety measures and awareness of soya and peanut cross-reactivity (Foucard et al. 2005). In recent years, anaphylaxis cases caused by soy protein are rare on a global level (Baseggio Conrado et al. 2021), no cases after exposure to low doses (<200 mg protein) were identified (FAO and WHO 2022c) although one case of fatal anaphylaxis has been reported from France (Poussel et al. 2019).

The expected rate of anaphylaxis among allergic individuals after exposure to soy at ED05 is 0 per 1 000 (95% CI 0 - 8) (Table 4) and the expected rate in the whole population is 0 (95% CI 0 - 4) per 100 000 infants/children and 0 (95% CI 0 - 1) per 100 000 adults (Table 4).

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