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Undeclared allergens in food – guide on how to assess the risk of allergic reactions in the population

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Preface

Scientific reports (e.g. risk assessments), published by the Swedish Food Agency (SFA), form the basis for risk management measures such as advice and information. Another important risk management measure is legislation. Allergens are partly managed by EU legislation. Labelling of allergenic ingredients, for example, is regulated by the Food Information Regulation (EU) No 1169/2011[1]. Food allergens may however occur undeclared in food products due to cross contamination. Even though food allergens are considered as hazards in hygiene regulation (EC) No 852/2004[2] there is currently no lower or upper thresholds for food allergens. Undeclared allergens can cause severe allergic reactions and as a dose-response relationship exists, an increasing number of consumers are expected to react.

This risk assessment guide offers comprehensive information regarding how SFA will assess the risk for allergic reactions in a population when analytical results regarding the concentration of an undeclared allergen are known. Food business operators and control authorities may also use the guide to calculate the risk undeclared allergens might constitute. This guide does not offer advice as to whether to take action or on which risk management decision to choose. Still, the guide is an important tool in aiding food business operators to make risk-based decisions regarding the handling of food allergens.

The first version of the risk assessment guide for food allergens was published by the Swedish Food Agency in 2015 (Livsmedelsverket, 2015). This second version was developed as additional research has been published regarding food allergens. It also follows the publication of the FAO/WHO summary report on reference doses for food allergens (FAO/WHO, 2021).

The guide has been written by Ylva Sjögren Bolin (PhD in immunology) and Eva Warensjö Lemming (PhD in nutrition). Jakob Ottoson (PhD in microbiology), Sanna Lignell (PhD in toxicology), Jessica Petrelius Sipinen (nutritionist) and Mia Hallgren (molecular biologist) have also contributed. The guide has been reviewed by Charlotte B. Madsen (emerita, Technical University of Denmark).

The Swedish Food Agency July 2022

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[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.

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Abbreviations

BMD	Benchmark Dose
BMDL	Lower limit of the confidence interval calculated for the benchmark dose
BMDU	Upper limit of the confidence interval calculated for the benchmark dose
DBPCFC	Double blind placebo-controlled food challenges - the gold standard method for testing whether an individual is allergic to a food. Can also be performed in order to test at which dose an allergic individual reacts. Forms the basis for calculating eliciting doses at population level.
DNA	Deoxyribonucleic acid
DTU	Technical University of Denmark
ED	Eliciting dose - The dose of protein (in mg) predicted to provoke reactions in a defined proportion of the allergic population (ED01, ED05, ED10etc.)
Efsa	European Food Safety Authority
ELISA	Enzyme-Linked Immunosorbent Assay
Epitope	The specific piece of the antigen (allergen) to which an antibody binds.
IgE	Immunoglobulin E, an antibody that is involved in allergic reactions
FAO	Food and Agriculture Organisation of the United Nations
FARRP	Food Allergy Research & Resource Programme, University of Nebraska (USA)
FSA	Food Standards Agency (UK)
LCI	Lower limit of a confidence interval
LOAEL	Lowest-observed-adverse-effect-level. The lowest tested dose that triggers an adverse reaction. Can both be used regarding an individual or regarding a population.
MED	Minimum eliciting dose. The lowest dose capable of eliciting an allergic reaction in an individual. Can sometimes also be called individual/clinical threshold or individual LOAEL.
NOAEL	No-observed-adverse-effect level. The highest tested dose that does *not* trigger an adverse reaction. Can both be used regarding an individual or regarding a population.
PAL	Precautionary Allergen Labelling
PCR	Polymerase Chain Reaction
TNO	Netherlands Organisation for Applied Scientific Research
UCI	Upper limit of a confidence interval
VITAL	Voluntary Incidental Trace Allergen Labelling
WHO	World Health Organisation

Sammanfattning

Odeklarerade allergener i mat - Guide för att bedöma risken för allergiska reaktioner i befolkningen utifrån ett analysresultat

I guiden beskrivs hur Livsmedelsverket beräknar risker, när allergener påvisas i livsmedel, utan att vara deklarerade i ingrediensförteckningen[3]. Guiden tar upp mjölk, jordnöt, hasselnöt, ägg, cashewnöt, valnöt, soja, vete, kräftdjur, fisk och selleri.

Du som livsmedelsföretagare, eller på en kontrollmyndighet, kan använda denna guide för riskvärdering. Det vill säga för att beräkna risker utifrån analysresultat, samt bedöma vilken risk ett kontaminerat livsmedel utgör, för allergiker, och för befolkningen i stort.

Det är livsmedelsföretaget som ansvarar för att det är säkert att konsumera de livsmedel som de producerar eller importerar. Allergener kan förekomma oavsiktligt, genom att livsmedel kontamineras. Allergener beskrivs som faror, i förordningen (EG) nr 852/2004[4]. Det finns dock i dagsläget inga gränsvärden för allergener. Kontrollmyndigheterna och företagen behöver därför bedöma riskerna innan de beslutar om eventuella åtgärder. Detta är en förutsättning för att minska omotiverat matsvinn, för att livsmedel ska bli säkrare för allergiker och för att allergiker inte ska vilseledas genom ogrundad ”Kan innehålla spår av…-märkning” .

Guiden beskriver dock inte vilka åtgärder som bör vidtas. Hänvisningar till åtgärder finns bland annat i Branschriktlinjer för allergi[5], Hygienförordningen[6] samt Codex Code of practice for allergen management[7].

Guiden anger utlösande doser för varje allergen

Varje allergent livsmedel beskrivs i var sitt kapitel, med utlösande doser (eliciting doses, EDs). Dessa beskriver andelen, som reagerar på en viss dos, av de som har allergi mot allergenet. Exempel: Vid dosen ED05 av mjölk, beräknas 5 procent av mjölkproteinallergiker reagera och 95 procent inte reagera.

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[3] Information om allergena ingredienser regleras av Europaparlamentets och rådets förordning (EU) nr 1169/2011 av den 25 oktober 2011 om tillhandahållande av livsmedelsinformation till konsumenterna.
[4] Europaparlamentets och rådets förordning (EG) nr 852/2004 av den 29 april 2004 om livsmedelshygien.
[5] Livsmedelsindustrins och dagligvaruhandelns branschriktlinjer för Allergi och annan överkänslighet – Hantering och märkning av livsmedel. Juni 2015.
[6] Europaparlamentets och rådets förordning (EG) nr 852/2004 av den 29 april 2004 om livsmedelshygien.
[7] Codex Code of practice for allergen management CXC 80-2020 FAO/WHO 2020.

Risken är högre, om en chokladkaka innehåller mjölkprotein vid en koncentration som motsvarar ED25, än om den innehåller jordnöt vid en koncentration som motsvarar ED05. Det beror på dels att fler personer beräknas reagera, dels på att fler bedöms reagera med svåra symtom vid en högre dos.

De utlösande doserna bygger på doser i vetenskapliga publikationer. Metodiken bakom beräkningarna av utlösande doser är gedigen. De bygger på födoämnesprovokationer som inkluderar allergiska patienter, både barn och vuxna, från många olika länder inklusive Sverige och övriga Europa.

Förslagen till referensdoser är inte beslutade

För varje allergen beskrivs även förslaget till referensdos – den hälsobaserade dosen som skulle kunna vara gränsen för krav om att sätta in åtgärder. Förslagen togs fram av en expertgrupp utsedd av FAO/WHO i augusti 2021. De baseras på ED05, alltså dosen där 5 procent av allergikerna reagerar, och 95 procent inte reagerar.

Livsmedelsverket anger däremot inte en specifik dos där man bör sätta in åtgärder vid en kontaminering. Livsmedelsverket kommer inte att själva besluta om referensdoser, eftersom det vore att föregå arbetet inom Codex och EU. Allergener är en risk som bör hanteras på global nivå.

Beräkna dosen utifrån analysresultatet

För att beräkna den dos allergen som allergiska personer kan få i sig, behöver man räkna med en sannolik portionsstorlek. Därför innehåller guiden också portionsstorlekar för flera olika livsmedel. Dessa är baserade på data från svenska matvaneundersökningar.

Om en kontaminering i ett livsmedel har konstaterats och det finns ett analysresultat av koncentrationen av allergenet, gör så här:

- Räkna fram dosen (i mg) genom att multiplicera analysresultatet (koncentrationen av allergenet, i mg/kg) med livsmedlets portionsstorlek (kg).
- Jämför dosen mot utlösande doser i guiden, för att bedöma hur allvarlig risken är.

Tänk på detta vid beräkningar och analyser av allergener

Följande aspekter är viktiga vid provtagning och analys av allergener. De beskrivs mer ingående i guiden.

Kontrollera analysmetoden

- Använd ett laboratorium som har en ackrediterad metod för det allergen som ska analyseras. Ackrediteringen ska även omfatta produkttypen – livsmedlet. För officiell kontroll är det ett krav att analysen är ackrediterad.

- Ha en dialog med laboratoriet om livsmedlet, dess bearbetning och ingredienser. Säkerställ att metoden kan påvisa allergenet även i upphettade livsmedel. Diskutera om det finns någon ingrediens som metoden kan korsreagera mot och därför ge ett falskt positivt resultat.

Kontrollera enheterna

- För att jämföra med utlösande doser (EDs), uttryck dosen i mg protein/kg. Var noga med hur provresultatet uttrycks – till exempel, anger värdet antalet mg jordnötsprotein/kg, eller mg jordnöt/kg?

Använd den mest relevanta portionsstorleken

- Portionsstorlekar från två svenska matvaneundersökningar, på vuxna respektive ungdomar, finns i tabell 5 i guiden. Använd portionsstorleken för den 75:e percentilen i beräkningar. Det motsvarar en stor portion. Använd den största portionsstorleken, om de två undersökningarna har olika värden.
- För livsmedel som säljs i Sverige, använd helst svenska data. För livsmedel som säljs i flera länder kan man använda data från andra länder, se exempel på referenser i guiden.

Beräkna dosen med följande formel:

dos (mg protein) = koncentration allergen (mg protein/kg) * portionsstorlek (kg)

Räkna med mätosäkerheten, se avsnittet Risk characterization.

Svårighetsgrad på reaktionerna

Allergiker är olika känsliga, i vilken dos som framkallar reaktion, men också i symtom. Vissa reagerar enbart med mildare symtom, medan andra kan reagera med milda symtom på en låg dos och med svåra symtom på en högre dos.

Allergiska symtom kan delas in i

- milda – illamående, hudutslag, magont, kliande munhåla
- medelsvåra – kräkning, väsande andning, omfattande hudutslag
- svåra – astma, anafylaktisk chock (allergisk chock, en svår allergisk reaktion som ger symtom från flera organ och kan vara livshotande)).

Det är viktigt att känna till att alla allergen som beskrivs i guiden kan orsaka svåra anafylaktiska reaktioner. De vanligaste orsakerna till anafylaxi och livshotande anafylaxi är dock jordnöt, mjölk, trädnötter och kräftdjur. Jordnöt är allra den vanligaste orsaken till anafylaxi. Mjölk var dock den vanligaste orsaken till dödsfall av anafylaxi hos barn i Storbritannien 1992–2018.

Summary

Food allergens are substances (often proteins) that commonly cause allergic reactions or other hypersensitivity issues. In food safety risk communication, as in this report, food that contains allergenic proteins (e.g., milk) are described as 'allergens' even though the specific food actually contains a number of different allergenic proteins. Allergens such as milk, peanut, or egg protein can go undeclared in food products due to mislabelling or contamination. Undeclared allergens can cause severe allergic reactions and a dose–response relationship exists, meaning that more allergic consumers will react if they are exposed to higher doses of the allergen. The symptoms of an allergic reaction vary from mild to severe and can involve one or several organs including the skin, the stomach, and the airways. The most severe symptom is anaphylactic shock, which can be fatal. Globally, peanuts, tree nuts, milk and crustaceans are the most common causes of anaphylaxis, including fatal anaphylactic shock.

Double blind placebo-controlled food challenges (DBPCFC) are the standard method for testing whether an individual is allergic to a food and can also be performed to test at which dose an allergic individual reacts. Data from individual DBPCFC can be used to calculate eliciting doses at the population level. Doses that elicit reactions in one to fifty percent of individuals allergic to milk, peanuts, hazelnuts, eggs, cashew nuts, walnuts, soy, wheat, shrimp, fish or celery, are described in this guide. The interval is collected from scientific publications.

Labelling of allergenic ingredients is regulated in the Food Information Regulation (EU) No 1169/2011[8]. Food allergens are considered hazards in Hygiene regulation (EC) No 852/2004[9] and food business operators therefore need to assess the risk of allergens and allergen cross-contamination in order to make risk-based decisions and take risk-based measures.

This risk assessment guide offers comprehensive information regarding how the Swedish Food Agency will assess the risk of allergic reactions in a population when the concentration of an undeclared allergen is identified. Food business operators and control authorities may also use the guide to calculate the risk undeclared allergens might constitute. The focus of the guide is on deterministic risk assessment, which offers a point estimate based on analytical results (mg/kg), food consumption data, and eliciting doses. Aspects to consider regarding analytical data, measurement uncertainty, food consumption data (portion sizes), and eliciting doses for different food allergens are included. In addition, the reference doses for food allergens proposed by FAO/WHO expert consultation on reference doses for food allergens

[8] 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.
[9] REGULATION (EC) No 852/2004 of the European Parliament and of the Council of 29 April 2004 on the hygiene of foodstuffs.

(FAO/WHO, 2021) are included. This report does not give advice as per which doses require actions, nor does it advise as to which risk management decision would be most appropriate in any given situation.

Introduction

Food allergens are food substances (often proteins) that commonly cause allergic reactions or other hypersensitivity reactions. Inadequate labelling of food allergens such as milk, egg and different nuts can cause severe health problems for allergic individuals. The symptoms of an allergic reaction vary from mild to severe and can involve one or several organs such as the skin, stomach and airways. The most severe symptom is anaphylactic shock, which can be fatal.

The labelling of allergenic ingredients is regulated by Food Information Regulation (EU) No 1169/2011[10]. Milk, peanut, hazelnut and egg are examples of allergens that are listed in Annex II of 1169/2011 and among those that, without exemption, have to be declared in the list of ingredients. A prepacked food that contains an undeclared ingredient listed in Annex II is classified as an unsafe food according to article 14.3 b in Regulation (EC) No 178/2002.[11,12] It is the responsibility of the food business operator that the food which it has imported, produced, processed, manufactured or distributed is safe for human consumption.

Undeclared allergens might occur in food products due to contamination. Food allergens are considered hazards in hygiene regulation (EC) No 852/2004[13]. They can be found in products placed on the market after food control involving sampling and analyses. Food business operators might also find allergens after analysis of either the final product or earlier in the process. This risk assessment guide offers comprehensive information regarding how the Swedish Food Agency will assess the risk for allergic reactions in a population when the concentration of an undeclared allergen is known. Food business operators and control authorities may also use the guide to calculate the risk undeclared allergens might constitute. An analytical result in a certain food is used to calculate a dose that one portion of that food contribute with. This dose can be compared to an eliciting dose to assess the risk for allergic consumers. Eliciting doses for milk, peanuts, hazelnuts, eggs, cashew nuts, walnuts, soy, wheat, shrimp, fish or celery are described. In addition, it includes reference doses as suggested by the FAO/WHO expert consultation (FAO/WHO, 2021).

[10] 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.

[11] Regulation (EC) No 178/2002 of the European Parliament and of the Council of 28 January 2002 laying down the general principles and requirements of food law, establishing the European Food Safety Authority and laying down procedures in matters of food safety.

[12] GUIDANCE ON THE IMPLEMENTATION OF ARTICLES 11, 12, 14, 17, 18, 19
AND 20 OF REGULATION (EC) N° 178/2002 ON GENERAL FOODLAW.
CONCLUSIONS OF THE STANDING COMMITTEE ON THE FOOD CHAIN AND ANIMAL HEALTH

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

The first version of the risk assessment guide for food allergens was published by the Swedish Food Agency in 2015 (Livsmedelsverket, 2015). It was developed to be used to assess the risk of undeclared food allergens in the Nordic control project - Undeclared allergens in food (Nordic Council of Ministers, 2016).

Risk assessment should incorporate four steps; hazard identification, hazard characterization, exposure assessment and risk characterization. Risk assessment as a part of risk analysis is further described in the Codex document (WHO/FAO, 2007). The important aspects to consider regarding risk assessment of food allergens; i.e. analytical results, food consumption and allergic reaction severity are described under the different steps of risk assessment. The four steps of risk assessment form the headlines in the report:

- Within **hazard identification** different allergens and the food categories they often are found in are described. How food allergens can be analyzed is also described under hazard identification. Recommendations regarding analyses and how to read an analytical report are also included.
- Within **hazard characterization** the symptoms a given food allergic reactions can give rise to are described. Consumers with allergies are per definition considered a risk group however, consumers that react to small amounts and/or manifest severe symptoms could be considered a risk sub-group to be assessed separately. This is further emphasized in the hazard characterization. The prevalence of certain food allergies as well as how many consumers that react to a certain dose are also described in the hazard characterization.
- The number of exposures are assessed within the **exposure assessment**. For this, food consumption data and results from laboratory analyses are used. The formula for this calculation is described in the methods section.
- **Risk characterization** describes the overall risk after incorporating the previous steps e.g. after hazard identification, hazard characterization and exposure assessment are considered together. The risk characterization further includes an uncertainty assessment.

A risk assessment can be qualitative, semi-quantitative or quantitative. This guideline has taken a quantitative approach.

After an overall description of food allergen risk assessment, separate chapters regarding different food allergens follow. These chapters describe the prevalence of the allergy, the symptoms and eliciting doses estimated to cause reactions in one to fifty percent of allergic consumers. The reference doses suggested by the FAO/WHO expert group are also included (FAO/WHO, 2021). In addition, certain aspects to consider regarding analyses of specific food allergen are described.

Aims and limitations

The aim of this report is to describe how the Swedish Food Agency performs a risk assessment when undeclared allergens (milk, peanuts, hazelnuts, eggs, cashew nuts, walnuts, soy, wheat, shrimp, fish or celery) are found in certain food products. The aim is also to assist food business operators and control authorities in making such risk assessments and thus to have basis for risk-based decisions. In addition, reference doses proposed after the FAO/WHO expert consultation are described (FAO/WHO, 2021). The aim of this report is also to discuss eliciting doses and globally suggested reference doses from a Swedish/Northern European perspective.

This risk assessment is restricted to IgE-mediated allergies. However, celiac disease and lactose intolerance are briefly described in the chapters about wheat and milk respectively. This risk assessment focuses on deterministic risk assessment and thus on analytical point estimates, food consumption data as well as eliciting doses.

The purpose of this risk assessment guide is not to describe a NOAEL (no-observed adverse-effect level) of allergens. The purpose is however to describe how calculations can be performed to investigate whether a certain food product contains proteins in concentrations that could lead to a dose that elicits reactions in one to fifty percent of the most sensitive allergic individuals (ED01 to ED50, respectively). ED01 to ED50 for different allergens are included in separate chapters. These ED:s are based on dose response mathematical models similar to Benchmark dose (BMD) calculations. BMD calculations are used in toxicology. Efsa has previously concluded that BMD calculations are a better approach than NOAEL to define a reference point (EFSA Scientific Committee et al., 2017). Different definitions, regarding allergen doses, are listed in Table 1 (EFSA Panel on Dietetic Products and Allergies, 2014, Madsen et al., 2020).

Action levels or regulatory thresholds (see Table 1) are not described. Such thresholds include risk management decisions and involves the acceptance of certain level of risk. The Swedish Food Agency will not precede legal work within Codex and EU and is thus only presenting examples as to how a risk assessment can be performed. Food business operators and control authorities can use the guide to calculate the risk undeclared allergens might constitute. Regarding whether to take action or which risk management decision to use e.g. cleaning, changing of supplier or labelling with Precautionary Allergen Labelling will not be advised upon in this guide. For further guidance the food business operators are advised to seek other guidance e.g. the Swedish Food Sector guidelines[14] or Codex Code of practice on allergen management for food business operators (CXC 80-2020).

[14] Swedish Food Sector Guidelines For: Management and labelling of food products with reference to Allergy and other Intolerance English Version, 2015

This guide only focuses on specific allergens listed in Appendix II of The Food Information Regulation (EU) No 1169/2011. The guide does not focus on risk assessment regarding allergenicity of novel food allergens.

Table 1. Terms used in risk assessment and risk management of food allergens. The table includes the Swedish Food Agency´s interpretation regarding whether the term is a risk assessment term or a risk management term.

	Description	Risk assessment term	Risk management term
NOAEL	No-observed-adverse-effect level. The highest tested dose that does *not* trigger an adverse reaction. Can be used on individual or population levels.	X	
LOAEL	Lowest-observed-adverse-effect-level. The lowest tested dose that does trigger an adverse reaction. Can be used on individual or population levels.	X	
MED	Minimum eliciting dose. The lowest dose capable of eliciting an allergic reaction in an individual. Can sometimes also be called individual/clinical threshold or individual LOAEL.	X	
Eliciting dose (ED)	The dose (mg protein) predicted to provoke reactions in a defined proportion of the allergic population (ED01, ED05, ED10etc.), derived from the dose distribution of individual minimum eliciting doses (MEDs). The suffix describes the proportion e.g. ED01= the dose predicted to provoke reactions in 1% of the at-risk allergic population.	X	
Reference dose	The dose (mg protein) derived from an acceptably low Eliciting dose (e.g. ED01, ED05) chosen as a health-based intake limit.		Risk management term since the decision regarding what constitutes an acceptable level of protection is a risk management decision.
Action level	The concentration (mg protein/kg) in food as it is consumed, containing the reference dose based on specified conditions of exposure (portion size etc).		X
Threshold (regulatory)	The maximum concentration of an allergenic protein deemed to pose a tolerable risk to the at-risk population, given their susceptibility and the circumstances of exposure e.g. 20 mg gluten/kg is the threshold for gluten in gluten free food. It may or may not be a population no (adverse) effect level.		X

Modified from (Madsen et al., 2020).

Methods

Aspects to consider when performing a risk assessment as described in the guide

This guide focuses on deterministic risk assessment. In deterministic risk assessment of food allergens *point estimates* of food consumption data, allergen concentrations and eliciting doses are used. The dose the allergic individual is exposed to depends on the concentration of the allergen protein in the compound food as well as the amount of food consumed. To calculate the dose (mg), allergen protein concentration data (mg/kg, obtained from chemical analysis) can be multiplied with food consumption data (portion sizes expressed in kg).

Allergen concentration (mg protein/kg) * Portion size (kg) = Dose (mg protein)

To be able to perform a deterministic risk assessment it is necessary to have access to analytical and food consumption data, as well as eliciting doses. In the following chapters recommendations regarding obtaining and analyzing such data are described.

- Analytical methods and their sensitivity i.e. limit of detection and analytical uncertainty are described under hazard identification.
- Eliciting doses based on double blind placebo-controlled food challenges (DBPCFC) are described in the separate chapters on different allergens.
- The dose to which a sensitive consumer is exposed is a product of the potion size times the concentration of the allergen in question. Portion sizes for several foods are described in the exposure assessment.

Details of search criteria and other aspects that describes updates from the first version of the Risk assessment guide

In order to write this revised version of the risk assessment guide the content in the previous risk assessment guide (Livsmedelsverket, 2015) was reviewed. In addition, a search for published references and scientific data published from 2015 was performed. This search was performed in the database PUBMED on 26 May 2021 using the words “food allergen risk assessment”, for the years 2015-2021. This search yielded 312 articles. The criteria for choosing certain articles is further described in Appendix 1 under search criteria.

Apart from the articles found during this search the Swedish Food Agency also used the following articles (Baseggio Conrado et al., 2021a, Baseggio Conrado et al., 2021b, Patel et al., 2021, Turner et al., 2021, Klein Entink et al., 2014). In April 2021 the Swedish Food

Agency published a report regarding Allergy and allergic cross-reactions to nuts, seeds, legumes, fruit and vegetables (Livsmedelsverket, 2021b) which is referred to in this report.

Further, the Swedish Food Agency arranged a workshop on risk assessment of food allergens in November 2020, together with the Technical University of Denmark (DTU). The Food Standards Agency (FSA, UK), the Netherlands Food and Consumer Product Safety Authority, the Netherlands Organisation for Applied Scientific Research (TNO) and Food Allergy Research & Resource Programme, University of Nebraska (FARRP, USA) were also part of the organising committee contributing to the planning and performing of the workshop. Presentations and discussions during that workshop also contributed to aspects considered in the revision of this guide.

Major changes compared to the previous version of the risk assessment guide (Livsmedelsverket, 2015) were the inclusion of more allergens (cashew nuts, walnuts, soy, wheat, celery, shrimp and fish). In addition, eliciting doses were updated (based on more DBPCFC and further refined calculations) and additional Eliciting doses were added (i.e. ED05, ED020, ED25 and ED50). Regarding food consumption data (portion sizes), results from a dietary survey in adolescents were included and additional foods were added. The inclusion of additional foods was requested by the Swedish food sector. Furthermore, the reference doses, as suggested after the FAO/WHO expert consultation for food allergens, were included. The disposition was modified to further mirror the different steps of a risk assessment described by Codex (WHO/FAO, 2007). Discrepancies to risk management were further described.

Portion sizes from two Swedish dietary surveys

Food consumption data is one important aspect in risk assessment of food allergens. As a food allergy is an acute reaction to intake of a food, the consumption data used in such a risk assessment should be data from one eating occasion (meal). Table 5 describes the median, 75^{th} and 95^{th} percentile of the amount of certain food products consumed by Swedish adults or adolescents during one meal (portion sizes). This consumption data is derived from two Swedish national dietary surveys performed on adults during 2010-2011 (Riksmaten vuxna 2010-2011(Livsmedelsverket, 2012)) and adolescents during 2016-2017 (Riksmaten ungdom 2016-2017 (Livsmedelsverket, 2018)), respectively.

In Riksmaten vuxna 2010-2011 participants (18-80 years) were recruited throughout the country from a random sample. Participants completed a dietary record for four consecutive days on the web and 1797 participants were included in the estimates. This method has been validated (Nybacka et al., 2016).

Riksmaten ungdom 2016-2017 was a school-based study in which participants (12-18 years) recorded their consumption of foods and beverages in a web-based method called RiksmatenFlexDiet (Moraeus et al., 2018), which has been shown to be valid for use in an

adolescent population (Lindroos et al., 2019). The consumption was recorded for three days, where day 1 and 3 were non-consecutive and retrospective. The second day was the day of the school visit and the day when participants provided blood samples and was consecutive to day 1. Day 3 was a random day occurring 3-9 days after day 2. For the present calculation participants that had completed all three days of recoding were included and the total sample was comprised of 2968 participants.

The surveys used two different web-methods with similar features. Both methods included a food list from which participants could choose the food consumed. Also, the portion setting was done by choosing portion sizes from pictures, household measures, and numbers of portions (cups, pieces, slices) or grams, also included in the method. Each food consumed was linked to a consumption occasion. To estimate portion size at each consumption occasion, the total amount consumed divided by the total number of eating occasions for each food was computed for each participant.

Hazard identification

"Hypersensitivity" refers to a repeatable adverse reaction to an allergen or other substance in food associated with an immune-mediated disorder (IgE-mediated food allergy, non-lgE mediated food allergy, celiac disease) or non-immune-mediated food intolerance (i.e. sulphites, lactose) (EFSA Panel on Dietetic Products and Allergies, 2014). The focus of this guide is IgE-mediated food allergies which can cause severe anaphylactic reactions including death. However, lactose intolerance and celiac disease are briefly described in the chapters about milk and wheat, respectively.

According to Efsa about 75 % of allergic reactions among children are due to eggs, peanuts, milk, fish and different nuts (EFSA Panel on Dietetic Products and Allergies, 2014). Allergy to crustaceans is one of the most common food allergies among adults. Wheat, soy, celery and different seeds have also been shown to be relatively common causes of food allergy.

Allergenic ingredients not listed in the list of ingredients or unintentionally present allergens, from contamination, can cause unexpected allergic reactions. The food products that most commonly have caused unexpected allergic reactions due to allergens being wrongly declared or due to contamination both in Sweden (Livsmedelsverket, 2011) and in the Netherlands (Blom et al., 2018) are:

- Chocolate/sweets
- Meat products (constituting part of a meal), e.g. meatballs.
- Ready-made meals (constituting a meal), e.g. lasagna.
- Bread, cookies and cakes

However, a large number of food products have been shown to be responsible for unexpected allergic reactions (Blom et al., 2018). Examples other than those included in the above listed categories are sauces, ice cream and fish products. Both in Sweden and in the Netherlands, milk is the allergen which causes the most unexpected allergic reactions (Livsmedelsverket, 2011, Blom et al., 2018).

The Nordic control project regarding undeclared food allergens in certain risk products (pre-packed chocolate/candy, bakery products, ready-made meals, and meat and fish products) showed that milk was detected in 12 percent of products without any declaration of milk (Nordic Council of Ministers, 2016). The product categories with undeclared milk were mainly chocolate/candy and bakery products. The concentrations of milk that were found in these products varied between 2.0 mg casein/kg to 2,600 mg casein/kg. Hazelnuts, peanuts, egg-white protein and gluten were found in 1.9, 1.1, 1.9 and 4.4 percent of products that contained no declaration of these allergens either as an ingredient or via Precautionary Allergen Labelling (PAL). The concentrations of these allergens varied between 31 to 130 mg

hazelnut/kg, 0.7 to 2.8 mg peanut/kg, 0.4 to 550 mg egg white protein/kg and 6.6 to 27 mg gluten/kg. Milk, peanut, and hazelnuts were more commonly detected in products labelled with PAL, compared to products without PAL. In products with PAL for specific allergens, the concentrations varied between 2.7 to 8,800 mg casein/kg, 3.1 to 18,500 mg hazelnut/kg and 0.7 to 42,500 mg peanut/kg. The highest concentrations of milk, hazelnuts and peanuts were found in certain chocolate products and it was calculated that more than 50 percent of allergic consumers would react to the doses found in those products. Egg white protein at 27 mg/kg and gluten at 6.4 mg/kg were found in one product each labelled with PAL for these allergens (Nordic Council of Ministers, 2016).

Analyses to identify undeclared allergens

Food allergens can be analysed with Enzyme-Linked Immunosorbent Assays (ELISA), via Polymerase Chain Reaction (PCR) or with mass spectrometry. The different methods targets protein, DNA or peptides and have different advantages and disadvantages (Holzhauser et al., 2020). ELISA is currently the most commonly used technique for allergen detection and quantification. One reason is that it is relatively easy and fast to use in a laboratory and that it targets allergenic proteins that are the elicitors of food allergies.

Recommendations regarding analytical results and uncertainties

Analytical challenges exist. It is therefore important to be aware of these challenges and to engage in dialogue with the laboratory. An accredited laboratory should be used for official control, and it is also advised that food businesses use accredited laboratories for their analyses. This is further described on the Swedish Food Agency´s website for the official food control (www.kontrollwiki.se). Accredited laboratories perform in-house validation of their methods and participates in proficiency tests designed to test their ability to accurately analyse a given analyte. The laboratory of the Swedish Food Agency take for example the recommendations from the Nordic Committee on Food Analysis (Nordic Committee on Food Analysis, 2009) and those from Abbot et al. (2010) into account when validating ELISA test kits and methods for food allergen analyses.

However, no reference methods are currently in place for analyses of food allergens (except gluten, see the separate chapter on wheat) (Holzhauser et al., 2020). Results can therefore differ between laboratories, accreditation notwithstanding. Neither targets (e.g. a specific peanut peptide), calibrants, nor reporting units are standardized. Currently there are only a limited number of reference materials available for allergen analyses. Despite this the use of reference doses is recommended as a driver of better analytical methods including targets and reference materials. This is further described in an article from official German food control laboratories (Waiblinger and Schulze, 2018)

The measurement uncertainty is often high when ELISA tests are used, and when compared to other kinds of chemical analyses. Methods are often based on propriety test kits with

monoclonal or polyclonal antibodies. Antibodies, particularly polyclonal antibodies and the test kits based on these, are subject to batch-to-batch variations. Further, the calibration standard is subject to batch-to-batch variations. The analytical method for casein has very high measurement uncertainty (Table 2) which in this case has been shown to be due to batch-to-batch variation (unpublished data Swedish Food Agency). Batch-to-batch variation means that different batches of ELISA test kits can give slightly different results.

Allergens can be in-homogenously distributed in the food products. This is especially common regarding nuts, seeds and legumes. Still, also other allergens can be inhomogenously distributed and a higher contamination might occur in the beginning of a batch of e.g. chocolate. It is important to consider how the allergens might be distributed when sampling is performed prior analyses.

Conclusions regarding analyses of food allergens

- Use an accredited laboratory (it is obligatory to use an accredited laboratory within official control).
- Engage in dialogue with the laboratory regarding processing and ingredients. Can the method detect also allergens in heated products? Is there any ingredient in food that the method might cause a cross reaction? For example, pea protein might give false positive results in a method that analyses peanut or soy.
- Be mindful regarding which unit the allergen is expressed in, e.g. mg peanut protein/kg or mg peanut/kg.
- Use protein in calculations in order to facilitate comparison to the EDs.
- Add the measurement uncertainty in the calculations (see Risk characterization).

Table 2. Analytes for which the Swedish Food Agency is accredited and performance of the methods used at the agency

Analyte	Type of analysis	LOQ	Measurement uncertainty[a]	Special consideration	Conversion factor to whole protein*
Casein	ELISA	≥0.5 mg/kg ≥2.5 mg/kg Depending on matrix	60 %	Caseins are heat-stable and thus suitable for analyses of milk protein but if whey fractions have been used casein analysis should not be performed.	1.2 (caseins constitute 80% of the milk proteins)
Egg (whole egg powder)	ELISA	≥0.5 mg whole egg powder/kg	45 %	Lysozyme is not detected.	0.45-0.49
Hazelnut	ELISA	≥2.5 mg/kg	55 %		0.16 (proteins constitute 16% of hazelnut flour)
Soy protein	ELISA	≥2.5 mg/kg	30 %		
Gluten	ELISA	≥ 5 mg/kg	30 %	Fermented foods should be analyzed with a competitive ELISA	1.2 (gluten constitutes 80% of the wheat proteins)
Walnut	ELISA	≥2.4 mg/kg	60 %		0.14 (proteins constitute 14% of walnuts)
Fish (raw cod)	ELISA	≥5 mg/kg	40 %	Less sensitive to some fish species e.g. salmon and anchovies. Heating and processing can also affect quantification.	0.18 (raw cod contains 18 % protein)

[a])Laboratories usually update measurement uncertainties annually. It is the measurement uncertainty of the methods at the Swedish Food Agency, calculated for 2022, that is described in the table. * General conversions factors have been collected from the article by (Holzhauser et al., 2020) for most food allergens. For walnut and fish (cod) data on protein content has been collected from the Swedish food database (Livsmedelsverket, 2021a). For egg protein a range is presented depending on figures presented by (Holzhauser et al., 2020) and the ELISA test kit manufacture R-biopharm (https://food.r-biopharm.com/). Gluten constitute approximately 80% of the total wheat proteins but differences between 70 to 90 % has been described (EFSA Panel on Dietetic Products and Allergies, 2014, Biesiekierski, 2017). Casein constitute 80 % of the total milk proteins (EFSA Panel on Dietetic Products and Allergies, 2014).

Hazard characterization

Allergic reaction symptoms and severity are described within the hazard characterization. A general description of allergic symptoms is described below. All allergens can cause these symptoms. Some allergens, however, are more likely to result in anaphylactic reactions and death which is described below and also in the separate chapters regarding different allergens. Vulnerable populations/specific risk groups (if known) are also described within the hazard characterization. Consumers with allergies are per definition considered a risk group however, the consumers that react to small amounts and/or with severe symptoms could be considered a risk sub-group to be assessed separately. The number of individuals within the population that might react is also described here. This number of consumers that might react is dependent on how common the allergy is within the total population but is also dependent on how many consumers react to a certain dose.

Symptoms and severity

Allergic individuals show high variability in allergic symptom/s and in doses to which they react. The symptoms of an allergic reaction vary from mild to severe and can involve one or several organs such as the skin, stomach and airways (Table 3). The most severe symptom is anaphylactic shock, which can lead to death. Anaphylactic shock means that the allergic individual suffers from a severe allergic reaction that induces symptoms from several organs. At least one of the symptoms has to come from the airways, and circulation or general condition needs to be severely affected in order for the reaction to be classified as an anaphylactic shock (The Swedish Association for Allergology)[15].

Table 3: Symptoms of allergic reactions

Organ	Symptom
Skin	Eczema, urticaria
Oral cavity, nose and eyes	Itching of the oral cavity, rhinoconjuctivites
Airways	Asthma, wheeze
Stomach	Pain, vomiting, diarrhoea
Multiple organs	Anaphylactic shock grade 1-3 (death)

[15] www.sffa.nu

A variety of factors contributes to reaction severity

- **Type of food allergen and severity:**

All food allergens can cause the symptoms described in Table 3 (Turner et al., 2016). This includes severe symptoms including anaphylaxis. Some differences exist however. These difference are further outlined in Table 4 which describes which food most commonly cause anaphylaxis or fatal anaphylaxis. This is also further described in each chapter regarding specific food allergens.

Peanuts and tree nuts are the most common causes of food-induced anaphylaxis, including fatal anaphylaxis, in both children and adults (Vetander et al., 2012, Baseggio Conrado et al., 2021a). Milk and eggs are also a common cause of anaphylactic reactions, especially among children. In the United Kingdom milk caused 26 percent of fatal anaphylactic reactions between 1992 and 2018 among children below 16 years (Baseggio Conrado et al., 2021a). Anaphylactic reactions to fish and seafood are slightly more common among adults compared to children. In Sweden fatal anaphylactic reactions have occurred to hazelnuts, soy, milk, peanuts and wheat (Foucard et al., 2005, Livsmedelsverket, 2021b).

Baseggo Conrado et al investigated which allergens most commonly cause severe reactions globally (2021b). These allergens are peanuts, tree nuts, milk and crustaceans. These food allergens are also the most common causes of fatal anaphylaxis (Turner et al., 2021). Other foods are a common trigger of severe reactions in one or two regions of the world (Baseggio Conrado et al., 2021b). Baseggio Conrado also investigated the relative frequencies of anaphylactic reactions in relation to the prevalence of the allergy. In Europe, cow´s milk and crustaceans cause a greater-than-expected proportion of anaphylactic reactions in children and adults, respectively. It is suggested that the explanation regarding milk is the lower awareness of cow´s milk as a potential cause of severe reactions as well as milk being a common ingredient in the Western-style diet and in processed food.

Table 4: Food allergens responsible for proportions of anaphylactic and fatal anaphylactic reactions among children and adults in Sweden and UK.

Food allergen	Anaphylactic reactions in Swedish children in 2007 in Stockholm (< 18 years, n=129) (Vetander et al., 2012)	Fatal anaphylactic reactions in UK children 1992-2018 (< 16 years)* (Baseggio Conrado et al., 2021a)	Fatal anaphylactic reactions in UK adults 1992-2018* (Baseggio Conrado et al., 2021a)
Peanut	14 %	14 %	20 %
Tree nuts	15 % (Cashew 5 %, Hazelnut 3%, Walnut 2 %)	9 %	9 %
Nuts unidentified	10 %	12 %	23 %
Milk	9 %	26 %	5 %
Egg	11 %		1 %
Fish and shellfish	5 %	6 %	7 %
Seeds	2 %		
Sesame seed	1 %		
Wheat	2 %		
Other	4 %	5 %	9 %
Mixed foods/ unidentified	26 %	29 %	26 %

*The total number of fatal anaphylactic reactions, among both adults and children, during these years were n= 187.

- **Dose of allergen.** The dose of an allergen affects the number of people that will react (further described below). In addition, it also appears that dose affects severity. However, data regarding this is scarce (Turner et al., 2016, Dubois et al., 2018).

  Peanut is the allergen that is most studied regarding dose and severity. A large clinical trial (Haber et al., 2021) found that median peanut individual LOAELs increase with response severity. The median value for mild reactions was 25 mg, for moderate reactions 44 mg and for severe reactions 133 mg of peanut protein. There was however overlap between categories. In the study (Haber et al., 2021) seven subjects (1.3 %) had severe reactions at doses below 5 mg peanut protein. Four of these did not react to 0.1-1 mg peanut protein. Three others were not challenged below 5 mg peanut protein. Of the total 548 challenges, 121 were classified as severe meaning that most severe reactions were due to challenges with well above 5 mg peanut protein.

  In the peanut allergen threshold study (PATS), single doses of peanut protein at 1.5 mg, the previous ED05 for peanuts, only reactions with mild to moderate severity were found (Hourihane et al., 2017). These reactions were urticaria, vomiting or rhinoconjunctivitis.

- **Food category (food processing and food matrix)**

  The epitopes of food allergens can either be linear or found within the three-dimensional structure of the protein. Allergenic activity may be influenced by food processing such as heating if the epitope is affected (Turner et al., 2016). One example of a food allergen which is destroyed by heating is Cor a 1, the birch pollen related hazelnut allergen. This epitope is within the three-dimensional structure of the protein. Most food allergens are however linear and stable and not destroyed by heating.

  A food matrix, the food ´s mixture/composition, might also effect the reaction severity (Turner et al., 2016). However, this does not occur to such an extent as to say, for example, that a higher fat content decreases overall risk.

- **Other aspects.** For health-care professionals and for allergic individuals it is important to consider other aspects that can influence the severity of an allergic reaction (e.g. previous reactions, exercise, alcohol, medication, stress etc) (Dubois et al., 2018). For the food industry and authorities, the type of food allergen, the type of food and the dose are the factors that could play a role regarding severity on a population level.

Prevalence

Data on prevalence describe the frequency of a specific allergy in the overall population and can be used to estimate risk. Prevalence regarding different allergenic foods is described in each chapter pertaining to specific allergenic foods.

Several uncertainties exist regarding prevalence numbers. The prevalence of allergy described in the chapters is based on studies in which the diagnosis has been set by oral food challenges or by doctor´s diagnosis combined with a test that analyses IgE-antibodies/sensitization. Studies based on self-reported data or sensitization only should not be used to estimate prevalence numbers (FAO/WHO, 2022b).

Differences in prevalence exist between geographical populations as well as between age groups (EFSA Panel on Dietetic Products and Allergies, 2014, FAO/WHO, 2022b). The prevalence data described in the different chapters is mainly based on studies performed in Europe. Differences in prevalence also occurs between different age groups. For some allergens certain age groups have not been thoroughly studied.

The expert group of FAO/WHO has summarized the global prevalence of food allergy (FAO/WHO, 2022b). The prevalence of food allergy is highest for peanuts, egg and milk. These allergies have a prevalence of more than one percent, in certain age groups, in two or more regions in the world. It is noteworthy that allergy to milk and egg is most common in young children (< 4 years of age). Allergy to crustacean shellfish, hazelnut and cashew nut/pistachio nut also occur within a relatively large proportion of the population. The prevalence for these allergies have been shown to be more than one percent in one region of the world and 0.5 to 1.0 % in at least another region of the world. Europe is among the studied regions.

Doses of proteins that trigger allergic reactions

Allergic individuals show high variability regarding which allergic symptom/s they develop, as well as to which doses they react. The doses of food allergens, e.g. milk protein and peanut protein, that different allergic individuals react to vary between micrograms and grams (EFSA Panel on Dietetic Products and Allergies, 2014). Double blind placebo-controlled food challenges (DBPCFC) are the standard method for testing whether a person reacts to a certain food and can also be used to test at which dose an allergic individual reacts. Data from DBPCFC can be used to calculate eliciting doses at both the individual level and at the population level.

Dose and population risk

The risk of allergic reactions in the population increases with dose. This is expressed as eliciting doses (ED) in which a suffix (e.g. 01) describes the proportion that might react. To describe this further some examples follow below:

- Doses below ED01 for e.g. milk protein are estimated to cause a reaction in less than one percent of milk allergic individuals.
- Doses at ED05 for e.g. milk protein are estimated to not cause a reaction in 95 % of the individuals allergic to milk protein. However, five percent of milk allergic individuals might react to this dose.
- Doses of milk protein above ED50 are estimated to cause a reaction in more than 50 percent of milk allergic individuals.
- Doses of milk protein between ED25 and ED50 are estimated to cause a reaction in 25-50 percent of milk allergic individuals.

The eliciting doses for different allergens are described in separate chapters further on in the report.

Methodology behind calculations of eliciting doses

The eliciting doses described in this report are collected from Remington et al (2020) and Houben et al (2020). The eliciting doses are based on an allergen threshold database in which public (published) and unpublished (hospital) data from challenge studies in allergic patients have been collected by TNO/FARRP (Netherlands Organisation for Applied Scientific Research and the Food Allergy Research and Resource Program at the University of Nebraska-Lincoln). The data and the database are further described by Westerhout et al. (2019). The challenge studies are designed to slowly increase the dose of an allergen delivered to an allergic individual until an objective reaction occurs. These dose-to-failure (response) studies are combined and analysed using parametric failure time models (i.e. mathematical models). This approach is similar to the Benchmark Dose (BMD) approach which is recommended by Efsa to use in toxicological risk assessment (EFSA Scientific Committee et al., 2017). Efsa also recommends the use of model averaging for deriving a

reference point from the critical dose–response data to establish health based guidance values and margins of exposure. A Bayesian "Stacked Model Averaging" for interval censored data have been used on the TNO/FARRP data. This model combines parametric survival estimated from multiple models into a single EDp estimation based upon a weighted average of survival estimates designed to estimate the true survival curve and the EDp estimations from the food allergen minimal eliciting dose (Wheeler et al., 2021).

The reference doses as suggested by the FAO/WHO expert consultation (FAO/WHO, 2021) are based on eliciting doses derived from the calculations from the TNO/FARRP database (Remington et al., 2020, Houben et al., 2020).

The database contains data for >3400 patients from several European countries (including Sweden), North and South America, Australia and Japan. Data exists for 35 different food allergens. For hazelnuts, milk, eggs and peanuts numerous individual data exist (411-1306). However, for the EU allergens lupine and sesame the number is much smaller (25-40). A study by Klein Entink et al investigated how many individual food challenges were needed for robust data regarding eliciting doses (2014). The study suggests that a sample size of $N \geq 60$ is required for obtaining stable EDp (eliciting doses on population level) estimates. Thus in this guide only ED for milk (450 challenged individuals), peanuts (1306 challenged individuals), hazelnuts (411 challenged individuals), eggs (431 challenged individuals), cashew nuts (245 challenged individuals), walnuts (74 challenged individuals), soy (87 challenged individuals), celery (82 challenged individuals), wheat (99 challenged individuals), shrimp (75 challenged individuals) and fish (82 challenged individuals) are included.

Mainly DBPCFC are included in the database and thus in the calculations regarding ED:s. However, some open challenges are also included for patients below 3 years of age (Westerhout et al., 2019). Symptoms after challenge are classified as objective or subjective. Objective symptoms are externally observable, e.g. urticaria or wheezing. Subjective symptoms cannot be confirmed by clinical observations e.g. itching in the mouth or chest tightness. The individual LOAELs were based on objective symptoms and objective symptoms are thus the basis for the EDs. The challenge doses were converted to milligrams of total protein of the allergenic food. Inclusion criteria were that challenges should include low doses with less than 1 mg protein being ideal. However, in some cases challenges below 10 mg or 100 mg protein were also included and were dependent on the type of allergen and amount of available data. The individual LOAELs can be expressed either as discrete or cumulative. A discrete LOAEL is based on the lowest dose that gave objective symptoms. A cumulative LOAEL includes all previous doses in addition to the dose that gave objective reactions. In this report EDs are most often based on discrete doses but when the cumulative doses were lower than discrete doses these were used instead.

Uncertainties regarding Eliciting dose

One of the uncertainties regarding Eliciting doses is that the most sensitive allergic consumers might not be challenged and thus are not included in the data. It is not known how many patients were excluded from the challenges or whether this could significantly affect published EDs. No uncertainty factors have been added to the ED:s. The FAO/WHO expert group concluded that no Margin of Exposure should be added to the ED:s (FAO/WHO, 2021).

Study-to-study heterogeneity regarding food challenges (i.e. different locations, different protocols) is one uncertainty. One difference between the studies can be the first dose that is administered. It is beneficial that this dose be as low as possible to receive data on individual LOAELs. As described above the ideal starting dose was below 1 mg protein but challenges below 10 mg or 100 mg were included in the challenge inclusion criteria. This is partly accounted for by classifying the data as left-censored in the challenges. This means that it is partly taken care of in the mathematical model (Wheeler et al., 2021).

Compared to the EDs in the previous version of the risk assessment guide, which is based on Taylor et al (2014) the methodology for calculating EDs has been recently improved by model averaging (Bayesian "Stacked Model Averaging") (Wheeler et al., 2021). Model averaging was recommended by Efsa 2017 in toxicological risk assessment using the BMD approach (EFSA Scientific Committee et al., 2017). By using model averaging study-to-study heterogeneity (i.e. different locations, different protocols etc.) is accounted for. Efsa also recommends that the BMD confidence interval should be reported rather than the value of the BMD. The lower bound (BMDL) is needed as a potential reference point according to Efsa. The confidence interval, with the lower confidence interval (LCI) and the upper confidence interval (UCI), is reported in the references Remington et al and Houben et al (Remington et al., 2020, Houben et al., 2020). The LCI-UCI are presented in the tables in the chapters describing the specific allergens in this report. The FAO/WHO mainly focused on the actual ED:s when presenting the reference doses but for some allergens the LCI were used. Efsa also writes that the upper bound (BMDU) is needed for establishing the BMDU/BMDL per ratio reflecting the uncertainty in the BMD estimate. Of note, the BMDU/BMDL ratio for milk and peanut at ED05 is 3.8 and thus reflects a quite low uncertainty. However, the BMDU/BMDL ratio for soy and walnut at ED05 is 25 and 89, respectively, and thus reflects a high uncertainty.

The food challenges in the TNO/FARRP database are more commonly performed on children compared to adults but it differs for different allergens. Cashew nut challenges have only been performed on children. For milk, eggs and wheat more challenges have been performed on children than on adults. However, regarding shrimp, fish and celery more challenges have been performed on adults compared to children. The differences in data between children and adults might not be a disadvantage since it partly reflects that different food allergies are more or less common in certain age groups.

One aspect that can skew data is whether challenged patients have a primary allergy or a milder cross reaction due to for example a birch pollen allergy. The symptom of this cross reaction is oral allergy syndrome. This can affect EDs, especially for hazelnuts if the patients are teenagers or adults from Northern Europe. Birch pollen allergy is very common in this region and thus cross reactions to hazelnuts in Northern Europe are also common (Livsmedelsverket, 2021b). It is therefore beneficial that the data comes from different countries (Europe, North and South America, Australia and Japan). Still, oral allergy syndrome is not classified as an objective symptom and is therefore probably not included as a reaction in the database.

A study by Haber et al (2021) also calculated EDs for peanut protein after 548 challenges on patients in the United States. They found a lower ED01 and ED05, at 0.052 and 0.49 mg respectively, compared to Remington et al (2020) and Houben et al (2020) at 0.2 and 2.1 mg respectively. Haber et al. discuss that several reasons could account for this difference. It is worth noting that they discuss whether a difference in populations could account for these differences, since Haber et al. only performed peanut challenges on patients in the United States. A proportion of peanut allergic patients might react to peanut due to birch pollen cross reactivity (Livsmedelsverket, 2021b). We speculate that the US population might have a higher proportion of primary peanut allergy than populations included in the TNO/FARRP database.

The Peanut Allergen Threshold (PATS) study (Hourihane et al., 2017) validated a predicted ED05 for peanut (1.5 mg peanut protein) by single doses. Of the 378 peanut allergic patients that were challenged, eight subjects met pre-fixed criteria for objective reactions. This means 2.1% instead of the predicted 5%. This could indicate that the predicted ED05 is rather conservative and not overly high. The peanut allergic patients came from three centres in Ireland, Australia and the USA and the recruitment process was performed in order to avoid recruitment biases e.g. to exclude patients which had previous severe reactions.

Food challenges are carried out in hospital settings with clinically well-managed patients. Patients might be more sensitive in other situations in every-day life. Individual factors such as stress, physical activity, alcohol consumption etc. might affect individual LOAEL. This is however something that health-care professionals should consider and may have less of an effect on the population level.

Exposure assessment

The exposure assessment describes how many will be exposed to the allergen and to which doses. The calculation described in the methods section is used. Food consumption data is important in these calculations as an integral part in reaching an estimate regarding how many individuals that will react to the food.

Food consumption data (portion sizes)

Food consumption data is one important aspect in risk assessment of food allergens. As a food allergy is an acute reaction to the consumption of a food, consumption data used should include portion size. Table 5 describes the median, 75th and 95th percentiles of the portion size of certain food products consumed by Swedish adults or adolescents. The portion sizes are derived from two Swedish national dietary surveys performed on adults 2010-2011 (Riksmaten vuxna 2010-2011(Livsmedelsverket, 2012)) and in adolescents 2016-2017 (Riksmaten ungdom 2016-2017 (Livsmedelsverket, 2018)). The methods section further describes how the calculations were performed.

Table 5. Portion sizes (g food/consumption occasion) from two Swedish dietary surveys on adults and adolescents, respectively.

	Adults N=1797, AGE=18-80 YRS, 4-DAY REGISTRATION				Adolescents N=2968, AGE=12-18 YRS, 3-DAY REGISTRATION			
Food	**Median gram**	**p75 gram**	**p95 gram**	**% Consumers**	**Median gram**	**p75 gram**	**p95 gram**	**% Consumers**
Chocolate and sweets	35	60	138	48	54	100	275	48
Bread	47	64	96	98	57	76	120	91
Soft bread	57	73	107	95	63	80	128	88
Crisp bread	19	24	39	60	18	28	42	34
”Sweet” bread*	50	76	136	73	60	92	180	47
Meatballs	84	116	210	27	90	128	225	33
Fish fingers	125	150	200	3	100	150	270	5
Sausages	68	100	198	55	70	130	213	38
Black pudding	120	160	240	3	100	150	250	11
Hamburgers	120	180	260	6	125	188	286	17
Pizza	390	600	600	18	310	500	670	25
Pie (main course)	200	200	400	12	200	300	523	4
Noodle wok	280	400	400	2	190	280	560	6
Casserole	200	225	400	30	188	225	450	34
Soup	300	350	500	29	225	300	550	27
Pancakes, waffles, crepes	180	240	420	15	195	260	450	18
Ready-made salad (meal e.g. chicken salad)	250	300	300	3.5	125	240	488	15
Fish gratin	250	350	450	3	150	250	450	6
Lasagne	350	500	500	8.5	350	400	700	14
Pie (dessert)	100	150	200	7.5	83	121	210	3
Pasta	113	175	250	46	113	175	263	56
Rice	140	175	280	29	175	175	315	49
Grains**	113	175	245	7	105	175	246	7
Breakfast cereals/muesli	30	43	90	50	30	45	100	44
Snacks (crisps etc)	30	60	150	20	40	84	200	33
Nuts/seeds	24	54	120	26	22	52	120	11
Mashed potato	203	293	383	21	203	293	406	20
Ketchup	20	40	70	22	25	35	71	34
Juice	200	250	375	42	210	315	520	42

	Adults N=1797, AGE=18-80 YRS, 4-DAY REGISTRATION				Adolescents N=2968, AGE=12-18 YRS, 3-DAY REGISTRATION			
Food	**Median gram**	**p75 gram**	**p95 gram**	**% Consumers**	**Median gram**	**p75 gram**	**p95 gram**	**% Consumers**
Plant-based milk substitute	n.d.				200	250	417	4
Wine	267	350	500	42	n.d.			
Beer	330	500	1300	33	n.d.			
Jam	34	45	80	47	40	58	130	35
Herring	30	45	68	10	20	30	60	0.2
Porridge	225	263	400	31	225	300	413	22
Ice-cream	63	90	150	31	70	104	185	21
Cheese (hårdost)	20	29	50	82	24	40	80	52
Dessert cheese	50	80	225	4	30	60	186	2

The median is presented instead of the average. The average was presented in the 2015 report.
* Sweet bread means buns, cakes, cookies
** In the group grains it was included food grains from wheat (including couscous and bulgur), rye, oat, barley, corn, buckwheat, quinoa and millet.
% Consumers presents the number of participants in the study that consumed the food on at least one occasion during the survey.
n.d. = no data or very little data and is therefore not representative.
The weights for all foods are presented as “ready to eat” i.e. for pasta, rice and grains the weights presented represent the boiled products and not the dry weight.

Aspects to consider regarding food consumption data including uncertainties

Consumption data differ between different surveys performed on different population groups and in different countries. From Table 5 it is obvious that there is difference in the amount of chocolate and sweets consumed between adults and adolescents. High-consuming adolescents (p95) consume twice the amount compared to adults. Also, the mean and p75 are considerably higher among adolescents. The percent of adults and adolescents that consumed “chocolate and sweets” during the days that the survey persisted is however the same (48 percent). On the other hand, regarding herring there is a large difference between the number of adult (10 percent) and adolescent (0.2 percent) consumers.

Blom et al (Blom et al., 2019) compared a deterministic risk assessment with a probabilistic risk assessment in order to study which point estimate of consumption is the best to use without leading to either under- or overestimation of risk. From this study p75 was suggested to be the optimal point estimate for use in deterministic food allergy risk assessment. The Technical University of Denmark use the p75 consumption data in the risk assessments performed on request from the Danish Veterinary and Food Administration

(Foedovarestyrelsen, 2018). The Swedish Food Agency recommends using the group with the highest p75 portion size. It might also be useful to look at how many consumers from each group had consumed the food during the survey. A food that is commonly consumed constitute a higher risk compared to foods that are less often consumed.

Observed differences, in consumption data, between different surveys may have several reasons; the dietary assessment method and whether it was completed by the participants or an interviewer, the number of recording days, misreporting by participants and the way portions (pictures, household measures, and numbers of portions (cups, pieces, slices) or grams) were represented in different surveys. This is influenced both by the portion size that is linked to a particular food as well as the ways in which the portion size is interpreted by participants. Furthermore, pictures vary by country, by layout and by the angles in which portions are viewed. One further challenge is that there may be differences in how food groups have been defined in different surveys. Further, the size of the dietary survey as well as the number of consumers that portion size calculations are based on will have an impact on the uncertainty of the portion size estimate (Nordic Council of Ministers, 2012, Nordisk Ministerråd, 2021). The context of the eating occasion, cultural differences and food packaging may also influence portion size. Whether dietary habits among the participants in the surveys are representative for the whole population is also important to consider. The Riksmaten adolescents (ungdom) 2016-2017 (Livsmedelsverket, 2018) provides valuable national data on diet, physical activity, and markers of exposure in age groups where data have historically been lacking. Participants were overall representative of the population with regard to socioeconomic background and school organization (public or independent) (Moraeus et al., 2018). For the survey performed on adults during 2010-2011, the proportion of participants born outside of Sweden was lower compared to the general adult population (Livsmedelsverket, 2012). Also, the proportion of participants with a higher education level was higher among participants than in the general population.

There are differences in food consumption data from the United States and the Netherlands. These differences lead to differences in allergen risk assessment outcomes (Meima et al., 2021). For 20 percent of the food groups the risk assessment outcome differed considerably. Examples of these food groups were alcoholic drinks, savoury salad, sandwiches and pizza. The authors conclude that it should be discouraged to use food consumption data from one country and extrapolate it to another country. However, data from most countries are not available when it comes to portion sizes. The study by Birot et al., 2018 combined food consumption data (portion sizes) from Denmark, the Netherlands and France. For some food groups it was easy to combine food data and for others the combined group was based on the subgroup with the highest consumption. This food consumption summary statistics per food group in Birot et al., (2018) can be compared to Swedish consumption data for risk assessment by companies that export food to countries outside Sweden. Meima et al., (2021) recommend using country specific data or to use the highest intake values if a risk assessment is meant to cover several countries.

Conclusions for using food consumption data:

- Use country-specific data if possible
- Use the 75th portion size percentile
- Use the survey with the highest 75th percentile portion size

Risk characterization

In risk characterization, hazard identification, hazard characterization and exposure assessment are all weighed together. The calculated dose (expressed as mg protein) is compared with the dose that elicits reactions within the interval one to fifty percent of the most sensitive allergic individuals (ED01 to ED50).

How the dose that leads to a reaction in for example five percent of the population correlates to contamination levels will depend on the amount of the food that is normally eaten. Below are some common foods that repeatedly are found to be contaminated with different allergens. The dose of allergen that represents ED01, ED10 or ED25 is combined with consumption to give a concentration of mg protein from allergenic food/kg food (Table 6). The reference dose suggested by the FAO/WHO expert consultation (mainly based on ED05) is presented for certain allergens and used in the calculations regarding the different food categories. As described previously in the document the Swedish Food Agency recommends adding measurement uncertainty to the concentration and to use the 75^{th} percentile regarding portion sizes. The Swedish Food Agency asserts that it is preferable to use these data since there are uncertainties within the analyses and in risk assessment and a slight overestimation compared to an underestimation, is preferable.

After calculating the percentage with a certain allergy that might react to a given allergen it is also important to consider the prevalence of the allergy in the total population in the calculation. An undeclared food allergen constitutes a higher risk if the allergy is more common within the population. A high exposure to for example milk protein at ED50, would cause a reaction in 50 percent of individuals allergic to this allergen. When assumed that this food allergy occurs with a prevalence of one percent in the overall child population, 1 out of 200 individuals in the pediatric population would react to that exposure. Allergy to celery or fish is less common than milk allergies. This means that in the total population, for example, ED05 of milk protein constitutes a higher risk compared to ED05 of fish or celery. In the chapter about milk, one hypothetical example regarding how to calculate the dose and the risk of undeclared milk is thoroughly described.

It is also important to consider symptom severity. A common misinterpretation regarding allergenic risks is that only peanut and nuts cause severe allergic (anaphylactic) reactions and deaths. As described within hazard characterization all food allergens associated with IgE-mediated food allergy can cause anaphylactic reactions and death. A chocolate bar containing a concentration of milk protein corresponding to ED25 constitute a higher risk compared to a

chocolate bar with peanut protein at a concentration which corresponds to ED01. This is both due to the fact that more people will be exposed to doses to which they will react (25 % compared to 1 %) and also since a higher dose can lead to a higher proportion of severe symptoms compared to a lower dose. In fact, milk was the most common cause of fatal anaphylactic reactions among children in the United Kingdom 1992 - 2018 (Baseggio Conrado et al., 2021a).

Table 6. Concentrations (mg protein from allergenic food/kg food) with included measurement uncertainty that equals the eliciting dose (ED01, ED10 and ED25) and the suggested Reference dose (RfD) for several food and allergen combinations based on the 75th consumption percentile.

Allergen	ED (mg)	Food	Consumption (p75) (kg)	Measurement uncertainty (Swedish Food Agency analytical methods)	Concentration causing reactions in 1, 10 and 25 % of allergic consumers[a] (mg protein/kg)	Comment
Milk protein	ED01: 0.2 RfD 2.0 ED10: 7.1 ED25: 32.7	Chocolate	0.100	60 %	C01+: 1.25 CRfD+: 13 CRfD: 20 C10+: 44 C25+: 204	Milk is among the food allergens that most commonly cause severe allergic reactions, including death, in children.
Hazelnut protein	ED01: 0.1 RfD: 3.0 ED10: 14.1 ED25: 95.5	Breakfast cereals	0.043	55 %	C01+: 1.5 CRfD+: 45 CRfD: 70 C10+: 212 C25+: 1433	Hazelnut is among the food allergens that most commonly cause severe allergic reactions, including death, in children and adults.
Peanut protein	ED01: 0.1 RfD: 2.0 ED10: 14.1 ED25: 95.5	Cake (sweet bread)	0.076	35 % (previous method)	C01+: 0.97 CRfD+: 19 CRfD: 26 C10+: 137 C25+: 928	Peanut is among the food allergens that most commonly cause severe allergic reactions, including death, in children and adults.
Soy protein[b]	ED01: 0.5 ED10: 41.9 ED25: 308	Plant-based milk substitute	0.25	30 %	C01+: 1.5 C10+: 129 C25+: 948	Can cause severe allergic reactions, including death, in children and adults.
Wheat protein	ED01: 0.7 RfD: 5.0 ED10: 15.4 ED25: 55.9	Soup	0.35	30 %	C01+: *1.5* CRfD+: 11 CRfD: 14 C10+: 34 C25+: 120	Can cause severe allergic reactions, including death, in children and adults. The ED:s and the critical concentration is expressed as wheat protein. The analyses are though often performed with methods detecting gluten. Gluten constitute 80 % of the total gluten proteins. Note that the concentration connected to ED01 is below the level of quantification of the method at 5 mg gluten/kg, corresponding to 6 mg wheat protein/kg.

[a] The concentration that equals the eliciting dose +, C01+ etc, has the included worst case measurement uncertainty included in the calculation. The concentration (x mg protein/kg) was calculated with the formula: X mg protein/kg * added measurement uncertainty * portion size (kg) = Dose (mg). For milk the concentration X mg protein/kg corresponding to ED01 is 0.2 mg milk protein/(1.6 * 0.100 kg) = 1.25 mg milk protein/kg. For the concentration corresponding to the suggested reference dose, CRfD, examples with the measurement uncertainty CRfD+ and without the measurement uncertainty CRfD are presented.

[b] No reference dose regarding soy protein has been suggested by the FAO/WHO expert group.

Milk protein allergy

Hazard identification and characterization

In this report, milk is defined as cow´s milk. Allergy to milk is an immune mediated reaction to milk proteins (reviewed in EFSA Panel on Dietetic Products and Allergies, 2014). Lactose intolerance is instead caused by undigested milk sugar (lactose) due to a lack of the enzyme that cleaves lactose (lactase). Individuals with milk protein allergies must avoid all milk products, including cheese. Individuals with lactose intolerance tolerate ordinary cheese and smaller amounts of other milk products.

Milk protein allergy is a serious condition. Even small amounts of milk proteins can elicit severe allergic reactions in allergic individuals (EFSA Panel on Dietetic Products and Allergies, 2014). Different kinds of milk allergies exists. The most common milk protein allergy is IgE-mediated allergy, in which the individual has IgE-antibodies to milk proteins and thus are sensitized to milk proteins. FPIES (Food Protein-Induced Enterocolitis Syndrome) is another type of allergy that can occur with milk. Also, other kinds on non-IgE-mediated allergy to milk occurs, especially among small children.

IgE-mediated allergy to cow´s milk affects approximately 0.6 to 1.6 percent of the population (FAO/WHO 2022b). The prevalence is highest in young age groups (children below 4 years of age) and lower in older children and adults. Only data based on food challenges and/or symptom + sensitization have been used in the prevalence estimates.

The symptoms of an allergic reaction can vary from mild to severe and involve one or several organs (EFSA Panel on Dietetic Products and Allergies, 2014). Symptoms from the stomach (stomach-ache, vomiting, diarrhea) and skin (eczema and urticaria) are common. The airways can also be involved with symptoms including asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, may occur. Among children, milk is the fourth most common food responsible for food-induced anaphylaxis (Vetander et al., 2012). Milk was the most common cause of fatal anaphylaxis among children in UK (Baseggio Conrado et al., 2021a). In Sweden, milk is the most common undeclared allergen to cause allergic reactions (Livsmedelsverket, 2011).

Doses of milk protein in relation to population risk

Overall allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to higher doses increases risk since a higher number of allergic individuals will react. ED01, ED05, ED10, ED20, ED25 and ED50 for milk protein are listed in table 7 (based on Houben et al (2020)). The clinical challenges, underlying the EDs of milk proteins, have mainly been performed in children. The reference dose as

suggested after the FAO/WHO expert consultation (FAO/WHO, 2022a) is also described below. It equals the ED05 but is rounded down to a whole figure.

Table 7. Dose that theoretically elicits reactions in 1 to 50 percent of milk allergic consumers, ED01 to ED50, including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020)

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Milk protein (mg)	0.2	2.0	2.4	7.1	13.8	22.2	32.7	125
LCI-UCI	0.1-0.5		1.3-5.0	3.8-14.2	7.5-26.7	12.3-42.5	18.2-61.8	70.1-227

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2022a)
If the analytical result is expressed as casein it should be multiplied by 1.2 since casein constitute approximately 80 percent of the total milk proteins. Thereafter this result can be compared to the ED:s for milk protein.

Methods for analyzing milk proteins

Caseins constitute about 80 percent of the proteins in milk. Caseins are heat stable and thus suitable for analysis of milk/milk proteins in food. The Swedish Food Agency is accredited to perform analysis of casein in most of the food products described in table 5. The method SLV-m141-f5 is an enzyme-linked immunosorbent assay (ELISA), which has a quantification limit of 2.5 mg casein/kg in some food products (e.g. bread) and 0.5 mg casein/kg in most food products e.g. chocolate/sweets. In table 7, ED:s are described as whole milk protein. If an analytical report gives the concentration of casein, a conversion factor of 1.2 (table 2) has to be applied to the analytical result.

Any analytical result is restricted to the sample analyzed. Milk can be un-homogenously distributed in a contaminated batch and thus sampling procedures are important. If the product is only contaminated with whey proteins a method that detects casein will not detect the contamination. A method that detects the milk allergen betalactoglobulin is better to use if the food is contaminated with whey protein as betalactoglobulin is the main part of whey proteins.

Example of a risk assessment: - undeclared milk in chocolate

Milk is not declared in the labelling of a dark chocolate bar, neither as an ingredient nor with precautionary allergen labelling. Laboratory analysis of the dark chocolate bar reveals that the sample contains 240 mg casein/kg. This is converted to milk protein by multiplying with the factor 1.2 since casein constitute 80 % of the proteins in milk (Table 2). The analytical result therefore corresponds to 288 mg whole milk protein/kg. When adding the measurement uncertainty of 60 % this equals 461 mg whole milk protein/kg. The 75th percentile of

chocolate consumption per meal is 100 g (0.100 kg) among Swedish adolescents. A person consuming 100 g of chocolate would thus be exposed to a dose of 46.1 mg whole milk protein. This is above ED25 but below ED50 for milk protein. The chocolate bar would thus be assumed to entail a risk of between 25 and 50 percent for milk allergic consumers. Assuming a prevalence of milk protein allergy of one percent among small children 250-500 out of 100 000 small children are expected to react to the chocolate bar. Chocolate and sweet consumption is common, at least among both adolescents and adults (Table 5).

Peanut Allergy

Hazard identification and characterization

Peanut allergy is an IgE-mediated allergy in which the individual has IgE-antibodies to peanut proteins and thus are sensitized to peanut proteins. IgE-mediated allergy to peanuts is one of the most common allergies globally (FAO/WHO 2022b). IgE-mediated allergy to peanuts affects approximately 0.2 to 1.6 percent of the population and is more common among children compared to infants and adults.

The symptoms of an allergic reaction can vary from mild to severe and involve one or several organs (EFSA Panel on Dietetic Products and Allergies, 2014). Symptoms from the stomach (stomach ache, vomiting, diarrhoea) and skin (eczema and urticaria) can occur as well as symptoms from the airways such as asthma and rhinitis. Systemic reactions, which might develop into an allergic (anaphylactic) shock, might occur. Among children, peanut is the food most commonly responsible for food-induced anaphylaxis in Sweden (Vetander et al., 2012). In United Kingdom peanut is the most common cause of fatal anaphylaxis among adults (Baseggio Conrado et al., 2021a).

Birch pollen allergic individuals might react with oral allergy syndrome to peanut. However, this clinical cross reactivity is lower compared to the cross reactivity between birch pollen and hazelnut.

Doses of peanut protein in relation to population risk

Allergenic risk increases with the symptom severity of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases risk since a higher number of allergic individuals will react. ED01 to ED50 for peanut protein are listed in Table 8 (based on Houben et al (2020)). The reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below. It equals the ED05 but is rounded down to a whole figure.

Table 8. Dose that theoretically elicits reactions in 1 to 50 percent of peanut allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020)

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Peanut protein (mg)	0.2	2.0	2.1	7.1	14.6	24.7	37.7	165
LCI-UCI	0.1-0.4		1.2-4.6	4.1-13.4	8.6-26.3	14.8-43.6	22.7-65.7	99.0-282

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021)
If the analytical result is expressed as peanut it should be multiplied by 0.25 since peanuts contain approximately 25 percent protein. Thereafter the result can be compared to the ED:s for peanut protein.

Method for analyzing peanuts

The Swedish Food Agency is currently not accredited to perform analyses of peanut but is planning to validate test kits in order to set up a method. Any analytical result is restricted to the sample analyzed. Peanut is often un-homogenously distributed in a contaminated batch and sampling procedures are thus important. Visual observations regarding whether pieces of peanut contaminate products might be equally important as analyses.

Hazelnut allergy

Hazard identification and characterization

Hazelnut allergy is an IgE-mediated allergy in which the individual has IgE-antibodies to hazelnut proteins and thus is sensitized to hazelnut proteins. Approximately 0.3 to 2.6 percent of the population in northern Europe are allergic to hazelnuts (FAO/WHO 2022b). The prevalence is higher among older children and adults compared to small children. IgE-mediated allergy to hazelnut is the most common food allergy in northern Europe. However, IgE-mediated hazelnut allergy can be divided into two different kinds of allergies, primary allergy or cross reactivity. The birch pollen allergen Bet v 1 is homologues to the hazelnut allergen Cor a 1 and is thus responsible for allergic cross reactivity. In northern Europe, a substantial number of individuals are allergic to birch pollen. Approximately 80 percent of hazelnut allergic individuals are sensitized to Cor a 1 and thus react to hazelnut due to cross reactivity with Bet v 1 (Datema et al., 2015). These people often react with only oral allergy syndrome: i.e. itching of the mouth and throat. The other kind of hazelnut allergy (primary allergy) is most often due to production of IgE-antibodies to other hazelnut allergens. This latter allergy is often of a more severe kind and symptoms might involve one or several organs. Symptoms from the stomach (stomach-ache, vomiting, diarrhoea) and skin (eczema and urticaria) can occur as well as symptoms involving the airways such as asthma and rhinitis (EFSA Panel on Dietetic Products and Allergies, 2014). Systemic reactions, which might develop into allergic (anaphylactic) shock, might also occur.

Even small amounts of hazelnut proteins can elicit severe allergic reactions in sensitized individuals. Among children who were treated for anaphylaxis in hospitals in the Stockholm area in 2007 hazelnut was responsible for three percent of these reactions. Hazelnut was thus the fifth most common food responsible for food-induced anaphylaxis (Vetander et al., 2012). Hazelnut could have been responsible for more anaphylactic reactions since unspecified nuts caused ten percent of reactions. Fatal anaphylaxis to nuts (unspecified) was the second most common cause of fatal anaphylactic reactions among adults in United Kingdom (Turner et al., 2016).

Doses of hazelnut protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk of a higher number of allergic individuals reacting. ED01 to ED50 for hazelnut protein are listed in Table 9 (based on Houben et al (2020)). The reference dose as suggested by the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below. It equals the ED05 dose but is rounded down to one whole number.

Table 9. Dose that theoretically elicits reactions in 1 to 50 percent of hazelnut allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020)

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Hazelnut protein (mg)	0.1	3.0	3.5	14.1	32.4	59.2	95.5	489
LCI-UCI	0.07-0.6		1.3-12-1	5.3-46.8	12.4-105	22.8-190	37.0-302	183-1400

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) If the analytical result is expressed as hazelnut it should be multiplied by 0.16 since hazelnuts contain approximately 16 percent protein. Thereafter the result can be compared to the ED:s for hazelnut protein.

Method for analyzing hazelnut

The Swedish Food Agency is accredited to perform analyses of hazelnut in the food products described in Table 5. The method SLV-m141-f2 is an ELISA which has a quantification limit of 2.5 mg hazelnut/kg which corresponds to 0.39 mg hazelnut protein/kg. Any analytical result is restricted to the sample that is analyzed. Hazelnut is often unhomogenously distributed in a contaminated batch and sampling procedures are thus important. Visual observations regarding whether pieces of hazelnut contaminate products might be equally important as analyses.

Egg allergy

Hazard identification and characterization

Allergies to eggs are most often caused by allergy to the proteins in the egg white. The most common egg allergy is IgE-mediated allergy, in which the individual has IgE-antibodies to egg white proteins and are thus sensitized to egg white proteins. It affects approximately 0.2 to 1.0 percent of the population (FAO/WHO 2022b). The prevalence is highest in young age groups (children below 4 years of age) and lower among older children and adults. Only data based on food challenges and/or symptoms + sensitization have been used in the prevalence estimates.

The symptoms of an allergic reaction can vary from mild to severe and involve one or several organs. Symptoms from the stomach (stomach ache, vomiting, diarrhoea) and skin (eczema and urticaria) are common. The airways can also be involved with symptoms including asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, might also occur. Under special circumstances, death has occurred. IgE-mediated allergy to eggs is one of the most common childhood allergies in Europe. Among children, egg is the third most common food responsible for food-induced anaphylaxis (Vetander et al., 2012). In Sweden, egg is the third most common undeclared allergen to cause allergic reactions (Livsmedelsverket, 2021b).

Doses of egg protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk since a higher number of allergic individuals will react. ED01 to ED50 for egg protein is listed in Table 10 (based on Houben et al (2020). The reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below. It equals the ED05 but is rounded down to a whole number.

Table 10. Dose that theoretically elicits reactions in 1 to 50 percent of egg allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020)

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Egg protein (mg)	0.2	2.0	2.3	6.3	11.8	18.5	26.7	94.5
LCI-UCI	0.1-0.5		1.2-4.7	3.4-12.6	6.5-22.9	10.4-35.5	15.0-50.5	53.1-173

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021)

Method for analyzing egg proteins

The Swedish Food Agency is accredited to perform analysis of egg proteins in the food products listed in Table 5. The method SLV-m141-f7 is an ELISA which has a quantification limit of 0.5 mg egg (whole egg powder)/kg. The result can be converted to egg protein by multiplying the result by 0.45 to 0.49 since whole egg powder contains approximately 45-49 % protein. Any analytical result is restricted to the sample that is analyzed. Egg can be unhomogenously distributed in a contaminated batch and therefore sampling procedures are important.

Cashew nut allergy

Hazard identification and characterization

Cashew nut allergy is an IgE-mediated allergy in which the individual has IgE-antibodies to cashew nut proteins and thus are sensitized to these proteins. Cashew nut (*Anacardium occidentale*) and pistachio nut (*Pistacia vera*) both belong to the family *Anacardiceae* (EFSA, 2014). Some individuals with allergies to cashews can cross react to pistachios.

The symptoms of an allergic reaction can vary from mild to severe and involve one or several organs (EFSA 2014). Symptoms from the stomach (stomach ache, vomiting, diarrhoea) and skin (eczema and urticaria) can occur as can symptoms involving the airways such as asthma and rhinitis. Systemic reactions, which might develop into an allergic (anaphylactic) shock, might occur. IgE-mediated allergy to cashew nuts affects approximately 0.01-0.2 percent of the population under 18 years in Europe but prevalence numbers above one percent have been shown in Australia (FAO/WHO, 2022b). Among children treated for anaphylaxis in the Stockholm area in 2007 cashew nuts were responsible for five percent of these reactions and pistachio nut for two percent (Vetander et al., 2012). Cashew nuts and pistachio nuts could, however, have been responsible for further reactions since unspecified nuts caused another ten percent of anaphylactic reactions.

Doses of cashew nut protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases risk since a higher number of allergic individuals will react. ED01 to ED50 for cashew nut protein are listed in Table 11 (based on Houben et al (2020)). The reference dose suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below. It equals the ED05 but is rounded up to one significant figure.

Table 11. Dose that theoretically elicits reactions in 1 to 50 percent of cashew nut allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	ED05	RfD FAO/WHO	ED10	ED15	ED20	ED25	ED50
Cashew nut protein (mg)	0.05	0.8	1.0	3.4	7.8	14.5	23.9	139
LCI-UCI	0.02-0.3	0.2-5.0		0.9-19.0	2.1-42.7	3.9-77.5	6.3-125	34.7-666

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021)
*If the analytical result is expressed as cashew nut it should be multiplied by 0.18 since cashew nuts contain approximately 18 percent protein. Thereafter the result can be compared to the ED:s for cashew nut protein.

Method for analyzing cashew nut

The Swedish National Food Agency is not accredited to perform analysis of cashew nuts at this time. However, other laboratories have for example ELISA for analyzing cashew nuts. An analytical result is restricted to the sample that is analyzed. Cashew nuts are often unhomogenously distributed in a contaminated batch and sampling procedures are therefore important. Visual observations regarding whether pieces of cashew contaminate products might be equally important as analyses.

Walnut allergy

Hazard identification and characterization

Walnut allergy is an IgE-mediated allergy in which the individual has IgE-antibodies to walnut proteins and thus are sensitized to these proteins. Walnut (*Juglans regia*) and pecan nut (*Carya illinoensis*) both belong to the family *Juglandaceae* (EFSA 2014). A substantial proportion of individuals with an allergy to walnuts cross react to pecan nuts. IgE-mediated allergy to walnut affects less than 0.5 percent of the population globally (FAO/WHO, 2022b). Still, walnut is classified as one of the more common food allergies globally.

The symptoms of an allergic reaction can vary from mild to severe and involve one or several organs (EFSA 2014). Symptoms from the stomach (stomach ache, vomiting, diarrhea) and skin (eczema and urticaria) can occur as can symptoms involving the airways such as asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, might occur. As with hazelnut, cross-reactivity to walnut might occur among birch allergic patients. Among Swedish birch pollen allergic patients 26 percent reacted to walnut with mild oral allergy syndrome (Biedermann et al., 2019). Among children treated for anaphylaxis in the Stockholm area in 2007, walnuts were responsible for two percent of these reactions and pecan nuts were responsible for 0.5 percent (Vetander et al., 2012). The nuts could however have been responsible for further reactions since unspecified nuts caused another 10 percent of anaphylactic reactions.

Doses of walnut protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases risk since a higher number of allergic individuals will react. ED01 to ED50 for walnut protein are listed in Table 12 (based on Houben et al (2020)). The reference dose as suggested after the FAO/WHO expert panel consultation is also described below (FAO/WHO, 2021).

Table 12. Dose that theoretically elicits reactions in 1 to 50 percent of walnut allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	ED05	RfD FAO/WHO	ED10	ED15	ED20	ED25	ED50
Walnut protein (mg)	0.03	0.8	1.0	3.8	9.7	19.3	33.5	235
LCI-UCI	0.01-0.5	0.1-8.9		0.6-35.0	1.5-81.1	3.1-152	5.5-252	37.8->1050

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) If the analytical result is expressed as walnut it should be multiplied by 0.14 since walnuts contain approximately 14 percent protein. (Livsmedelsverket, 2021a). Thereafter the result can be compared to the ED:s for walnut protein.

Method for analyzing walnut

The Swedish Food Agency is accredited to perform analyses of walnut in the food products described in Table 5. The method is an ELISA which has a quantification limit of 2.4 mg walnut/kg which corresponds to 0.34 mg walnut protein/kg. The method also detects pecan nuts. Any analytical result is restricted to the sample that is analyzed. Walnut is often unhomogenously distributed in a contaminated batch and sampling procedures is therefore important. Visual observations regarding whether pieces of walnut contaminate products might be equally important as analyzes.

Soy allergy

Hazard identification and characterization

Allergies to soy are often IgE-mediated. FPIES (Food Protein-Induced Enterocolitis Syndrome) can also be caused by soy. IgE-mediated allergy to soy affects less than 0.5 percent of the population globally (FAO/WHO, 2022b). The symptoms of an IgE-mediated allergic reaction can vary from mild to severe and involve one or several organs (EFSA 2014). Symptoms from the stomach (stomach ache, vomiting, diarrhea) and skin (eczema and urticaria) are common. The airways can also be involved with symptoms such as asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, might also occur. Under special circumstances, death has occurred.

Soy (*Glycine max*) is a legume just like peanuts, peas and beans. Cross-reactivity to soy can occur among peanut allergic individuals and vice versa. A clinical cross reactivity of around 1-15 percent has been suggested (EFSA Panel on Dietetic Products and Allergies, 2014, Cabanillas et al., 2018). Also, birch pollen allergic individuals might react with oral allergy syndrome to soy. However, this clinical cross reactivity is much lower compared to the cross reactivity between birch pollen and hazelnut.

In Sweden, several severe allergic reactions have occurred when peanut allergic individuals have reacted to soy protein in for example meat products. Four deaths of children between 9-17 years occurred in which soy was the most probable cause (Foucard et al., 2005). The children all suffered from asthma. The doses of soy protein that caused the fatal anaphylaxis described above were all high. In one example, one hamburger contained two percent soy protein (Foucard et al., 2005). However, none of the anaphylactic reactions that occurred in the Stockholm area during 2007 were due to soy (Vetander et al., 2012).

Doses of soy protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk of a higher number of allergic individuals reacting. ED01 to ED50 for soy protein are listed in Table 13 (based on Houben et al (2020)).

Table 13. Dose that theoretically elicits reactions in 1 to 50 percent of soy allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	ED05	ED10	ED15	ED20	ED25	ED50
Soy protein (mg)	0.5	10.0	41.9	99.1	186	308	1780
LCI-UCI	0.2-3.5	2.2-54.6	10.6-192	27.1-419	53.4-748	91.1-1200	547-6460

Method for analyzing soy

The Swedish Food Agency is accredited to perform analyzes of soy in the food products described in Table 5. The method is an ELISA which has a quantification limit of 2.5 mg soy protein/kg. The method cross-reacts to some legumes, for example red lentils and yellow peas. Any analytical result is restricted to the sample that is analyzed.

Celery allergy

Hazard identification and characterization

Celery (*Apium graveolens*) can be consumed cooked or raw or dried as a spice (EFSA Panel on Dietetic Products and Allergies, 2014). Also, the seeds of celery can be used as a spice. The symptoms of an IgE-mediated allergic reaction can vary from mild to severe and involve one or several organs. Symptoms from the stomach (stomach-ache, vomiting, diarrhea) and skin (eczema and urticaria) are common. Airways can also be involved with symptoms such as asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, might also occur.

Allergy to celery can be primary but it can also be caused by clinical cross reactivity among individuals with allergies to birch or mugwort (EFSA Panel on Dietetic Products and Allergies, 2014). Allergy to celery affects less than 0.1 percent of the population globally (FAO/WHO, 2022b).

Doses of celery protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk since a higher number of allergic individuals will react. ED01 to ED50 for celery protein are listed in Table 14 (based on Houben et al (2020)). The doses are based on the discrete doses except for ED01, ED05 and ED10 that are based on the cumulative doses since these are lower.

The protein content in celery spice is approximately 4.5 times higher compared to raw celery (EFSA Panel on Dietetic Products and Allergies, 2014). This means that lower amounts of celery spice gives symptoms compared to raw celery.

Table 14. Dose that theoretically elicits reactions in 1 to 50 percent of celery allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	ED05	ED10	ED15	ED20	ED25	ED50
Celery protein (mg)	0.05	1.3	5.4	13.0	23.3	36.9	180
LCI-UCI	0.02-0.5	0.2-7.9	1.2-28.3	3.3-55.8	6.2-89.9	10.3-134	55.2-596

Method for analyzing celery

The Swedish Food Agency is not accredited to perform analysis of celery. Celery is often analyzed using PCR. When analyses are performed with PCR, which measures celery DNA, it is important to receive information from the laboratory regarding how to recalculate the results for celery protein.

Wheat allergy

Hazard identification and characterization

Celiac disease and allergies to cereals e.g. wheat allergy are two different diagnoses (EFSA Panel on Dietetic Products and Allergies, 2014). The immune system is involved in both disorders.

Celiac disease or gluten intolerance is an immune mediated disease triggered by gluten proteins present in wheat, rye and barley (EFSA Panel on Dietetic Products and Allergies, 2014). These gluten proteins cause an inflammation of the mucosa in the small intestine leading to flattening of the mucosa and, when the illness is untreated, to malnutrition. Celiac disease is a life-long, permanent intolerance to gluten. The prevalence of Celiac disease is around 0.5 to 1 percent in Europe (EFSA Panel on Dietetic Products and Allergies, 2014). However, it might be higher in certain countries and the prevalence in Sweden is more likely to be around 1.5 – 2 percent (Browaldh et al., 2014).

Cereals like wheat, rye and barley must be excluded from the diet of individuals with celiac disease. As alternatives, products labelled “gluten-free” or “very low gluten” can be used. The “gluten-free” products are often based on i.e. maize, rice, oat, millet or buckwheat. The products labelled “gluten-free” or “very low gluten” can also be based on cereals, which have been rendered gluten-free, such as wheat starch. Additional information regarding this labelling can be found in Commission regulation (EU) No 828/2014 and on the website of the Swedish Food Agency.

Proteins from wheat (and other cereals), including gluten, can also cause IgE-mediated allergic reactions (EFSA Panel on Dietetic Products and Allergies, 2014). Such reactions are immediate or delayed after ingestion and their severity varies from mild to very severe, in some cases anaphylaxis. One type of IgE-mediated wheat allergy is exercise-induced anaphylaxis in which anaphylaxis can occur if ingestion of wheat occurs close to exercise. IgE-mediated allergy to wheat affects less than 0.5 percent of the population globally (FAO/WHO, 2022b).

Doses of wheat protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk since a higher number of allergic individuals will react. ED01 to ED50 for wheat protein and gluten are listed in Table 15 (based on Houben et al (2020)). The reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below.

These doses are restricted to IgE-mediated allergy to wheat. There is a threshold for labelling products “gluten-free” and thus for products suitable for people with celiac disease. The threshold is 20 mg gluten/kg. Rules for labelling foods as "gluten-free" and "very low gluten" are given in Commission regulation (EU) No 828/2014.

Table 15. Dose that theoretically elicits reactions in 1 to 50 percent of wheat allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Wheat protein (mg)	0.7	5.0	6.1	15.4	26.9	40.3	55.9	174
LCI-UCI	0.3-2.5		2.6-15.6	7.1-35.9	12.8-59.6	19.7-86.9	27.6-118	87.7-344

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021)
If the analytical result is expressed as gluten it should be multiplied by 1.2 since gluten constitute approximately 80 percent of total wheat proteins. Thereafter the result can be compared to the ED:s for wheat protein.

Method for analyzing wheat protein (gluten)

The Swedish Food Agency is accredited for analysis of gluten in food including fermented foods such as beer. Gluten is often used as a marker for total wheat proteins. Gluten constitute approximately 80% of the total wheat proteins but differences between 70 to 90 % have been described (EFSA Panel on Dietetic Products and Allergies, 2014, Biesiekierski, 2017).

In the Codex standard 118-1979, revised in 2008, general criteria for analyzing gluten is described. Also, the enzyme-linked immuno assay (ELISA) R5 method is listed as a method for determining gluten concertation. The limit of quantification is 5 mg gluten/kg (ppm). The quantification limit is not low enough to detect concentrations of gluten that can cause reactions in one percent of the most sensitive wheat allergic consumers when food that are consumed in large quantities are analysed.

PCR methods can be used to analyze whether the gluten comes from wheat, barley and/or rye.

Shrimp/Crustacean allergy

Hazard identification and characterization

Allergy to shrimp is more common among adults compared to children (EFSA 2014). The prevalence is estimated to be 0.1-1.5 percent of the European population (FAO/WHO, 2022b). The prevalence is higher in children and adults compared to small children. People with an allergy to shrimp often cross-react to other crustaceans such as crab and lobster (EFSA 2014). Cross-reactivity to molluscs such as oyster and octopus can occur. Crustaceans and molluscs are called shellfish. Cross-reactivity can also occur to edible insects (Ribeiro et al., 2018). Certain proteins that are similar between species within the phylum *Arthropoda*, to which both insects and crustaceans belong, cause this cross reactivity.

The symptoms of an IgE-mediated allergic reaction can vary from mild to severe and involve one or several organs (EFSA 2014). Symptoms from the stomach (stomach-ache, vomiting, diarrhoea) and skin (eczema and urticaria) are common. The airways can also be involved with symptoms such as asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, might also occur. Reactions due to cross-reactivity can be severe including symptoms such as asthma and anaphylaxis. Crustaceans are one of the most common causes of anaphylaxis globally (Baseggio Conrado et al., 2021b).

Doses of shrimp protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk of a higher number of allergic individuals reacting. ED01 to ED50 for shrimp protein are listed in Table 16 (based on Houben et al (2020)). The reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below. It equals ED05 but is rounded down to one significant figure.

Table 16. Dose that theoretically elicits reactions in 1 to 50 percent of shrimp allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Shrimp protein (mg)	26.2	200	280	723	1260	1880	2580	7910
LCI-UCI (mg)	2.7-166		69.3-880	268-1900	560-3090	907-4460	1290-6030	3760-17900

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021)

Method for analyzing shrimp (crustacean tropomyosin)

A muscle protein, tropomyosin, is one of the proteins that are similar between species within the phylum *Arthropoda* to which both insects and crustaceans belong. ELISA-methods, in which antibodies are directed towards for example shrimp tropomyosin exist. The antibodies, and thus also the ELISA, often cross-reacts with tropomyosin from other crustaceans. The Swedish Food Agency does analyze shrimp (crustacean tropomyosin) but is not accredited. If an analytical result is expressed in tropomyosin, ask the laboratory for a conversion factor to whole shrimp protein.

Fish allergy

Hazard identification and characterization

Allergy to fish is less common than allergy to shrimp in the general population (EFSA 2014). The prevalence is less than 0.5 percent and most likely to be around 0.1 percent (FAO/WHO, 2022b).

The symptoms of an IgE-mediated allergic reaction can vary from mild to severe and involve one or several organs (EFSA 2014). Symptoms from the stomach (stomach-ache, vomiting, diarrhoea) and skin (eczema and urticaria) are common. The airways can also be involved with symptoms such as asthma and rhinitis. Systemic reactions, which might develop into allergic (anaphylactic) shock, might also occur. Fish can provoke severe anaphylactic reactions and death has occurred (EFSA 2014).

Parvalbumin is the major fish allergen and belong to the second (after tropomyosin) largest animal food allergen family (EFSA 2014). It is a muscle protein, and it is found in all fish species. Cod parvalbumin is used both in tests for sensitization to fish and as a marker for fish when analysing food for fish protein. Parvalbumins have been shown to be the only fish allergen that 95 % of patients allergic to fish react to. Parvalbumin expression differs between fish species and white fish muscle expresses more parvalbumin than dark muscle. Albacore tuna thus appears to be less allergenic. Hake and cod are examples of fish species which more frequently are allergenic.

Doses of fish protein in relation to population risk

Allergenic risk increases with the severity of the symptoms of a reaction as well as with the number of individuals who might react. On a population level, exposure to a higher dose increases the risk of a higher number of allergic individuals reacting. ED01 to ED50 for fish protein are listed in Table 17. The doses are based on the discrete doses presented via reference Houben et al (2020) except for ED01 that is based on the cumulative dose since this is lower. The reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021) is also described below. It equals the low confidence interval of ED05 (4.5) but is rounded up to one significant number.

Table 17. Dose that theoretically elicits reactions in 1 to 50 percent of fish allergic consumers (ED01 to ED50), including lower and upper confidence interval (LCI, UCI). Data from Houben et al. (2020).

	ED01	RfD FAO/WHO	ED05	ED10	ED15	ED20	ED25	ED50
Fish protein (mg)	1.3	5.0	12.1	26.7	45.5	69.2	99.1	418
LCI-UCI (mg)	0.4-12.7		4.5-43.9	10.2-88.7	17.6-143	27.0-210	38.8-293	163-1150

RfD FAO/WHO is the reference dose as suggested after the FAO/WHO expert consultation (FAO/WHO, 2021)

Method for analyzing fish

The Swedish Food Agency is accredited for analyzing fish protein in food with ELISA. The method is directed towards cod parvalbumins. As described above the expression of parvalbumins differs between different species and the detection limit and quantification limit is thus different for different species. This is important to consider when analyzing food for undeclared fish protein. Cod contains approximately 18 percent protein (Livsmedelsverket, 2021a) and this can be used a conversion factor if the result is expressed as cod and not as fish protein.

Other food allergens

Food allergens such as lupin, sesame, almond and mustard can also cause severe allergic reactions and are also listed in appendix II of the Food information regulation (EC) no 1169/2011. However, the number of DBPLFC to these allergens are lower compared to the previously described allergens. According to the study by Klein Entink et al. (2014) at least 60 food challenges should be performed and used as datasets in order for ED data to be robust. Published doses regarding other allergens than those thoroughly described in this guide are thus not as robust and special care should be taken when using this data as calculations with that data involves further uncertainties.

The FAO/WHO expert consultation has suggested provisional reference doses for almond at 1.0 mg almond protein (FAO/WHO, 2021). The also suggest a reference dose of 2.0 mg sesame protein/kg (FAO/WHO, 2022a).

Conclusions

This guide reviews the science behind risk assessment of food allergens. Undeclared allergens can constitute a health risk for allergic individuals. Allergens can be present undeclared in food due to mislabeling or due to contamination. A dose-response relationship for allergens exists on a population level meaning that if an allergic population is exposed to higher doses, more individuals will react compared to if they are exposed to lower doses. Symptoms of allergic reactions can vary from mild to severe anaphylactic reactions. Globally, peanut, tree nuts, milk and crustaceans are the most common causes of anaphylactic reactions, including fatal anaphylactic reactions.

Risk assessments regarding undeclared food allergens such as milk proteins can be made via deterministic risk assessment. A deterministic risk assessment provides a single point estimate regarding risk. An IgE-mediated allergic reaction is an acute reaction caused by food consumption. Portion sizes of different foods vary. Therefore, a quantitative analytical result (i.e. a concentration) needs to be recalculated to the dose allergen (milligrams) contained in a single meal of a certain food. Thereafter, the calculated dose is compared to the eliciting dose (ED), which is the dose that elicits allergic reactions in one to fifty percent of the most sensitive allergic individuals (ED01 to ED50). Theoretically, a calculated dose corresponding to ED01 of milk can cause an objective allergic reaction in one percent of the milk allergic population. Similarly, a dose corresponding to ED01 is estimated to not cause an objective reaction in 99 percent of the same population. Further, a dose corresponding to ED25 of milk is estimated to cause a reaction in 25 percent of milk allergic individuals, and so on.

The Swedish Food Agency agrees with the FAO/WHO expert consultation (FAO/WHO, 2021) in basing the reference doses/eliciting dose on available challenge data from allergic persons. In addition, the Swedish Food Agency agrees that the data reported in the publications of (Remington et al., 2020) and (Houben et al., 2020) are the most comprehensive and best described sources available to date. Still, the Swedish Food Agency will not precede legal work within Codex and EU. As a consequence a wide range of eliciting doses (ED01 to ED50), including confidence intervals are presented, together with the suggested FAO/WHO reference doses based on ED05.

This report also describes existing uncertainties within different parameters of deterministic risk assessments, for example analytical data, food consumption data and EDs. Therefore, it is recommended to use an accredited laboratory for food allergen analysis, to use worst case measurement uncertainties and to use the 75:th percentile regarding the food consumption data.

This guide describes how the Swedish Food Agency performs risk assessment of food allergens from an analytical result. Food business operators and control authorities can also use the guide to calculate the possible risk potential of undeclared allergens. It is important to

consider the risk magnitude of a certain food allergen when making risk-based decisions and measures. For example, a chocolate bar containing milk protein at a concentration corresponding to ED25 constitutes a higher risk than a chocolate bar with peanut protein at a concentration corresponding to ED01. This is because more allergic individuals will be exposed to doses to which they will react to (25 percent compared to 1 percent) and a higher dose may lead more severe symptoms compared to a lower dose.

This guide does not advise whether to act based on the risk assessment or which risk management measure to use, such as more extensive equipment cleaning, changing suppliers or labelling with Precautionary Allergen Labelling (PAL). For further guidance, Food business operators are advised to seek other guidance in specific Swedish Food Sector guidelines[16], other Food Sector guidelines or in the Codex Code of practice on allergen management for food business operators (CXC 80-2020).

[16] Swedish Food Sector Guidelines for Management and labelling of food products with reference to Allergy and other Intolerance June 2015

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Appendix 1 Search Criteria

Search performed in Pubmed https://pubmed.ncbi.nlm.nih.gov/ May 26 2021:”Food allergen risk assessment”, years 2015-2021.

Results: 312.

Articles that investigated risk assessment of any of the allergens listed in appendix II of Regulation (EU) no 1169/2011 were considered. As were articles describing severity of allergic reactions. Also, articles investigating food consumption data in connection to risk assessment were considered. Articles investigating or describing risk assessment of novel foods or patient/health care risk assessment were not included. Altogether 12 of the 312 results were included in the guide.

This risk assessment guide offers comprehensive information regarding how the Swedish Food Agency will assess the risk for allergic reactions in a population when the concentration of an undeclared allergen is identified. The allergens described in this report are milk, peanut, hazelnut, egg, cashew nut, walnut, soy, wheat, shrimp, fish and celery. Food business operators and control authorities may also use the guide to calculate the risk undeclared allergens might constitute. The guide is an important tool in aiding food business operators to make risk-based decisions regarding the handling of food allergens, although it does not offer advice as to whether to take action or on which risk management decision to choose.

Livsmedelsverket är Sveriges expert- och centrala kontrollmyndighet på livsmedelsområdet. Vi arbetar för säker mat och bra dricksvatten, att ingen konsument ska bli lurad om vad maten innehåller och för bra matvanor. Det är vårt recept på matglädje.

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