



Symptoms at population Eliciting Doses $\leq$ ED05 for 11 priority allergenic foods are mild to moderate

W. Marty Blom^{a,b,*}, Joost Westerhout^a, Thuy-My Le^b, Steve L. Taylor^c,
Joseph L. Baumert^c, Geert F. Houben^{a,b}

^a TNO, The Netherlands Organisation for Applied Scientific Research, Utrecht, the Netherlands

^b University Medical Center Utrecht, Utrecht University, the Netherlands

^c Food Allergy Research and Resource Program, University of Nebraska, Lincoln, USA

ARTICLE INFO

Handling Editor: Dr. Bryan Delaney

Keywords:

Allergic symptoms
Eliciting Dose
Food allergen
Reference Dose
Risk assessment
Severity

ABSTRACT

Insight into symptoms at low doses of protein from priority allergenic foods may support decision making and acceptance of harmonized reference doses for Precautionary Allergen Labeling (PAL). Symptoms were extracted from double-blind placebo-controlled food challenges underlying the full range Eliciting Dose (ED) distributions (Houben et al., 2020). Frequency and severity were analyzed at and below doses to which a maximum 10% of the allergic population is predicted to respond with objective symptoms (ED10). Detailed symptom descriptions at every dose were recorded for 1102 food challenges with 11 allergenic foods. At doses $\leq$ ED10, generally, 1 to 2 symptoms, either objective or subjective, occurred per positive challenge (average 1.8 ± 1.2 , range 1–8). Symptoms were mostly (68%) subjective of nature. Most objective symptoms were in the skin (60–71%; e.g. flush, erythema), followed by eyes/nose and oral cavity (rhinorrhea, red eyes, lip swelling). Far less symptoms (approx. 5–8%) occurred in the gastrointestinal (vomiting) and respiratory tract (cough). Symptoms were graded mild to moderate, except for 2 cases of a severe symptom (wheeze, laryngeal edema), which occurred at a dose above the ED05 (approximately the ED08). Exposure $\leq$ ED05 of priority allergenic foods resulted only in mild to moderate symptoms in a small proportion of the allergic population.

1. Background

Avoidance of the offending allergenic food is crucial for allergy management by food allergic individuals. In many countries, labeling regulations are in place to specifically indicate the presence of priority allergenic foods when they are used as ingredients in the finished product formulation, but the voluntary labeling of the possible unintended presence of allergens in food products (precautionary allergen labeling - PAL) is unclear and inconsistent (Allen et al., 2014; Allen and Taylor, 2018). Unexpected reactions to food products frequently occur in the allergic population and can be severe to potentially life threatening (Michelsen-Huisman et al., 2018; Versluis et al., 2015). This situation leads to uncertainty and anxiety in allergic patients that considerably affects their quality of life (Lange, 2014; Warren et al., 2020).

Food allergic patients and healthcare professionals struggle with understanding PAL on food products, largely because there is no general agreement for standards and phrasing for PAL (DunnGalvin et al., 2015;

Holleman et al., 2021). Reference doses for risk based action levels are increasingly recommended for deciding on the need or not for applying PAL (Brooke-Taylor et al., 2018; FAO and WHO, 2022; Taylor et al., 2014). The reference doses are based on low doses predicted to elicit objective allergic symptoms in a specified proportion of the allergic population (Houben et al., 2020; Remington et al., 2020). The Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022) recently recommended using the ED05 (the dose predicted to elicit objective allergic symptoms in 5% of the allergic population) as a basis for deriving Reference Doses. They based these on the ED05 of the population ED distribution (Houben et al., 2020; Remington et al., 2020), noting that the data reported in the publications of (Remington et al., 2020; Houben et al., 2020) were the most comprehensive and best described source (i.e. the TNO-FARRP threshold database) available, both in terms of content and curation, with supportive peer-reviewed publications. The dose-distribution analysis methodology was similarly well-described for this dataset.

Acceptance of Reference Doses by all stakeholders involved will benefit from insight into the severity of a possible reaction at the low ED

* Corresponding author. TNO, The Netherlands Organisation for Applied Scientific Research, Utrecht, the Netherlands.

E-mail address: marty.blom@tno.nl (W.M. Blom).

<https://doi.org/10.1016/j.fct.2025.115250>

Received 14 November 2024; Received in revised form 9 January 2025; Accepted 9 January 2025

Available online 11 January 2025

0278-6915/© 2025 The Authors. Published by Elsevier Ltd. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

Abbreviations

ATDB	Allergen Threshold Database
DBPCFC	double-blind placebo-controlled food challenges
ED	Eliciting Dose
LOAEL	lowest observed adverse effect level
RD	Reference Dose
PAL	Precautionary Allergen Labeling

range (DunnGalvin et al., 2015; Madsen et al., 2020). A complicating factor in discussions is that severity is a relative and subjective expression with multiple definitions. Which allergic symptoms are considered a severe reaction varies among and within different stakeholder groups (Dubois et al., 2018; Stockhammer et al., 2020; Turner et al., 2016). For instance, anaphylaxis often is thought to be a serious life-threatening event, but anaphylaxis is not one single unique allergic symptom. Anaphylaxis constitutes a spectrum of symptoms ranging from mild to severe (Cardona et al., 2020; Turner et al., 2019), and at least 80% of anaphylactic reactions will resolve without treatment (Turner et al., 2022). Although it is generally accepted that there is a hierarchy of risks for food allergic individuals ranging from very minor symptoms, e.g. tingle or itch to mild moderate symptoms and severe to life threatening symptom (Dubois et al., 2018; FAO and WHO, 2022), there is no general standard for grading symptoms (Arasi et al., 2021; Eller et al., 2018; Fernández-Rivas et al., 2021; Purington et al., 2018; Shah et al., 2023). Published classification systems rank allergic reactions for example into mild, moderate and severe, or provide a further 5-step grading or also numerical systems (Zhu et al., 2015; Eller et al., 2018; Fernández-Rivas et al., 2021; Purington et al., 2018; Shah et al., 2023). In general, the published classifications have a strong focus on identifying anaphylaxis and need for treatment and describe severity for only part of possible symptoms in an allergic reaction.

At the low ED range of the threshold dose distribution, a small proportion of the population is expected to experience at most mild to moderate objective symptoms (Remington et al., 2020; Taylor et al., 2014). Single dose studies validating the ED05 for peanut and milk confirmed this (Hourihane et al., 2017; Turner et al., 2021). A systematic review and meta-analysis of published diagnostic and immunotherapy studies focusing on the possible risk for anaphylaxis showed that of those individuals reacting to the ED05 level of peanut, approx. 5% could potentially develop an anaphylactic reaction (Patel et al., 2021). Further, the anaphylactic reactions occurring in this dose range varied considerably and many will be a mild anaphylactic reaction resolving without any treatment (Turner et al., 2022). However, a clear description of the particular symptoms that food allergic patients may experience at and around proposed ED05-based reference doses is currently lacking. The present study investigates all symptoms recorded in the TNO-FARRP threshold database occurring at doses $\leq$ ED10 for the priority allergenic foods for which population threshold dose distributions have been reported (Houben et al., 2020; Remington et al., 2020). Evaluation of the type of symptoms, including the severity, will give insight into the overall health consequences for the allergic population that may experience an allergic reaction at these dose levels, and as such, is aimed to contribute to characterizing the safety and residual risk of reference doses based on low ED values.

2. Materials and methods

2.1. Database

The database used for the present study has been described in detail elsewhere (Remington et al., 2020; Houben et al., 2020). Briefly, the database contains over 3400 individual threshold data from low-dose

food challenge studies in food allergic patients that were systematically collected by the Netherlands Organisation for Applied Scientific Research (TNO) and the Food Allergy Research and Resource Program (FARRP) of the University of Nebraska-Lincoln, USA. For each individual patient, the lowest observed adverse effect level (LOAEL) is defined based on the first objective symptoms of an allergic response occurring and the no observed adverse effect level (NOAEL) is set at the previous dose in the clinical protocol (Westerhout et al., 2019). A dose is recorded in milligrams of total protein from the allergenic food (Taylor et al., 2014). Data from double-blind placebo-controlled food challenges were included in the Allergen Threshold Database (ATDB) if the author/s/clinics clearly reported the LOAEL for objective reactions, the dosing scheme used and indicated if/when repeated doses were used, detailed the challenge material, and reported the symptoms in an individual fashion or reported a grouped symptom classification with a clear separation between objective and subjective symptoms (Westerhout et al., 2019). Symptom descriptions at the NOAEL and LOAEL in the ATDB therefore range from indicating “subjective/objective symptoms”, grouped symptom or organ classifications (e.g. skin, oral cavity), severity scorings such as Sampson or Mueller classifications, to the detailed signs and symptoms as described in Westerhout et al. (2019) occurring at each dose step of the challenge.

2.2. Data extraction and analyses

2.2.1. Inclusion of challenge data for the study

Challenge data were included if each dose was accompanied with a detailed description of the specific symptoms and if the first received dose was $\leq$ ED10 for the allergenic food. Challenges were excluded when the details of symptoms could not be deduced; these were challenges for which the NOAEL and LOAEL were reported as objective allergic reaction, but without any specification of the symptoms reported at each dose at the individual patient level. In the original publications, symptoms or a severity score of the food allergy may have been mentioned, but these often could not be related to a specific individual patient and/or its threshold dose; or, symptoms were summarized for the organ systems involved or summarized in a severity classification such as Sampson or Mueller, or individual symptoms were provided as a summary for a patient without indication at which dose these were actually happening, which means that (part of) the symptoms reported for this patient may have occurred at different doses. In all such cases data were sufficiently detailed to deduce that an objective symptom occurred at a specific dose for inclusion in the database (i.e. for the NOAEL and LOAEL). But the actual symptoms present at the individual dose for the patient are missing and these cases could not be included in the current analyses.

2.2.2. ED values

For the present study, the cut off values were the ED01, ED05 and ED10 for the cumulative threshold dose distribution of 14 allergenic foods (Houben et al., 2020; Remington et al., 2020). The cumulative and discrete ED values are given in Supplement Table S1.

2.2.3. Symptoms

Multiple clinical expressions were present to describe the same symptom and the dataset was therefore harmonized into the symptom descriptions as described in Westerhout et al. (2019) to facilitate the analysis. For instance, *stomach pain* was renamed as *abdominal pain/gastric pain*. *Dizzy* and *vertigo* all became *dizziness*. Other examples were *panic* or *upset* which were renamed *tension/agitation*, or *facial swelling* which became *angioedema*. Part of the data summarized the subjective symptoms of the oral cavity as oral allergy syndrome (OAS). Symptoms were assigned independently by two authors WMB and JW, all newly assigned symptoms were discussed and approved by a clinician (TML). Because possible gradings for a symptom were not consistently reported in original datasets, this grading was removed, e.g. *mild cough* became

Table 1Characteristics of the dataset in the dose ranges $\leq$ cumulative ED10 for allergenic foods.

	$\leq$ ED01	ED01- $\leq$ ED05	ED05- $\leq$ ED10	$\leq$ ED10
All food challenges (FC) included in the initial analysis with sufficient detail on symptoms, not necessarily symptoms $\leq$ ED10^{a)}				
# FC with at least one dose in the dose range	286	1013	919	1102
FC with first dose in the dose range	286 (26%)	733 (66.5%)	83 (7.5%)	1102
Allergenic foods	6 cashew, celery, fish, hazelnut, peanut, shrimp	11 all	10 all but shrimp	11
FC receiving at least one dose in the dose range AND presenting symptoms within the dose range^{a)}				
FC with symptoms (% of total FC in the dose range)	68 (24%)	273 (27%)	260 (28%)	444 (40%)
Allergenic foods	5 celery, fish, hazelnut, peanut, shrimp	11 all	11 all	11
Classification of individual symptoms				
Total nr of symptoms listed ^{b)}	109	480	503	1092
Subjective/ objective symptoms	65%/35%	73%/27%	64%/36%	68%/32%
Number of different classified symptoms reported	18	40	43	46
Classification of the allergic reaction				
Average number of symptoms reported per FC ($\pm$ s.d.)	1.6 $\pm$ 1.2	1.8 $\pm$ 1.1	1.9 $\pm$ 1.3	1.8 $\pm$ 1.2
Range of number of symptoms per FC	1–6	1–6	1–8	1–8
Patients with objective LOAEL ^{c)}	11 ^{c)}	42 ^{c)}	48 ^{c)}	101
Allergenic foods of the LOAEL ^{d)}	2 celery, peanut	6 cashew, egg, hazelnut, milk, peanut, walnut	10 cashew, celery, egg, fish, hazelnut, milk, peanut, shrimp, wheat, walnut (not soy)	10 cashew, celery, egg, hazelnut, milk, peanut, shrimp, wheat walnut, (not soy)

^{a)} Age and gender characteristics are provided in [Supplement Table S3](#).^{b)} Symptoms, especially mild subjective symptoms could occur at multiple doses within an ED range, and/or also spanning 2 dose ranges. Only unique symptoms in a dose range are indicated and counted, but could be repeated in the next dose range. Further, multiple symptoms may occur in the same individual.^{c)} The distribution of LOAELs in each of the dose ranges: at the range $\leq$ ED01 11 patients had their LOAEL for objective symptoms (1.0%); 53 patients (5.3%) at the range $\leq$ ED05; and 101 patients (9.2%) at $\leq$ ED10.^{d)} LOAELs were present for various allergenic foods ([Supplement Table S4](#)).

cough or localized urticaria became urticaria. In total 188 unique symptom descriptions were classified into 46 signs or symptoms (see [Supplement Table S2](#)). For 4 of the symptoms, it was unclear to which harmonized sign or symptom it should be linked, but it was related to the organ, these were spot/pimple mouth (Oral cavity), feeling of pressure around eyes (Eyes and Nose), sweat (Skin), and itchy feeling at the height of sternum (Respiratory tract). For 17 subjective symptoms the description was unclear; indicating “subjective symptom” (n = 12) or incomplete description like cold, recognizing peanut (n = 3).

2.2.4. Categorization in ED ranges

All reported symptoms for a single dose in a clinical study (in mg total protein of the allergenic food) were categorized into 3 different ED ranges: $\leq$ ED01, ED01- $\leq$ ED05, ED05- $\leq$ ED10 for the respective allergenic food. Patients could have symptoms occurring in multiple ED ranges. In case the same symptom occurred in multiple ED ranges, this symptom was counted in all ED ranges in which the symptom occurred.

2.2.5. Classification of symptoms

Symptoms were classified for being subjective or objective ([Westerhout et al., 2019](#)). Grading of the individual symptoms as mild, moderate or severe was as described in [Supplement and Table S2](#) for the full list of symptoms and their classification. There is no consensus on the grading of individual symptoms although for part of the symptoms there is more general agreement regarding being mild, moderate or severe than others ([Arasi et al., 2021](#); [Eller et al., 2018](#); [Zhu et al., 2015](#)). None of the available grading systems can be applied one to one to all the symptoms and signs listed by [Westerhout et al. \(2019\)](#), which are the symptoms noted for the food challenges in our database and used in the

present analyses. Further, because none of the available grading systems are regarded as the golden standard for classifying symptoms, we considered it not appropriate to modify the symptom descriptions in our dataset according to the symptom description of either one of the grading systems. In addition, selection of one grading system will lead to losing a significant part of the symptom details. Therefore, grading of the individual symptoms as mild, moderate or severe was performed on the basis of classifications systems described in various publications ([Ben-Shoshan et al., 2010](#); [Cardona et al., 2020](#); [Cox et al., 2010](#); [Kimchi et al., 2015](#); [Muraro et al., 2007, 2018](#); [Purington et al., 2018](#); [Zhu et al., 2015](#)) and as described in the [Supplementary Table S2](#). It was not the intention to review all available opinions or to develop a new scoring system, but to provide a grading that would reflect the general view and would allow an evaluation of symptom severity at low ED ranges of protein from allergenic foods. The general view was applied and usually a conservative approach was taken, i.e. in case of doubt a more severe category was assumed.

2.3. Statistics

Descriptive statistics using Excel was used to analyse the occurrence and frequency of symptoms.

3. Results

3.1. Food challenges included

For 1102 food challenges, patients received at least one dose $\leq$ ED10 and detailed information on symptoms at each dose of the challenge was

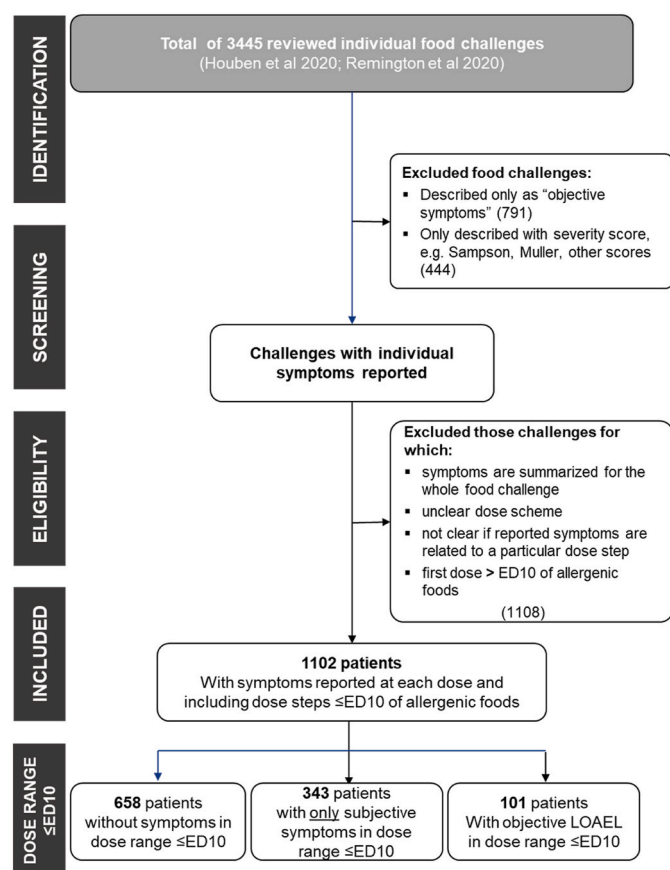


Fig. 1. Flow chart of food challenge inclusion in the study. The dataset is extracted from the 3445 reviewed individual food challenges underlying the population threshold distributions for 14 priority allergens reported previously (Houben et al., 2020; Remington et al., 2020).

present (Fig. 1, Table 1). These data were from adults and children, 13 countries throughout Europe (15 clinical centers), and available for 11 allergenic foods (cashew ($n = 244$), celery ($n = 41$), egg ($n = 99$), fish ($n = 26$), hazelnut ($n = 165$), milk ($n = 131$), peanut ($n = 308$), shrimp ($n = 27$), soy ($n = 14$), walnut ($n = 41$) and wheat ($n = 6$). This data subset covered a third of the full dataset (1102 out of 3445 FC) and a similar proportion for each of the allergenic foods, except for 2 extremes; almost all challenges with cashew (244 out of 245 FC) fulfilled the selection criteria to just 6% of the FC for wheat (6 out of 99 FC). The median population age was 7.7 yr (0.3–72.5 yr) with slightly more males (46.6%) than females (33.1%), and for 20.3% sex was not provided (Supplement Table S3 for details). 92.5% of the patients received their first dose $\leq$ ED05, and 7.5% in the range ED05– $\leq$ ED10. For 101 out of 1102 food challenges (9.2%), the objective cumulative LOAEL occurred in the dose range $\leq$ ED10, which is close to the 10% that could be expected (Table 1, Supplement Table S4 for the different allergenic foods).

3.2. Food challenges with symptoms $\leq$ ED10

Symptoms, either objective or subjective, at doses $\leq$ ED10 were observed for 42% of food challenges ($n = 444$), whereas for the other 658 food challenges, symptoms were present from higher doses onwards ($>$ ED10). As we also analyzed the nature of subjective symptoms, the percentage of symptoms occurring was higher than the expected percentage for objective reactions only (i.e. ca 10% at the ED10). The majority of the reported symptoms $\leq$ ED10 indeed were subjective in nature (70%) (Table 1). For each of the 3 ED ranges, approximately a similar proportion of the patients experienced symptoms (24–28%), which were primarily subjective and occasionally an objective

symptom. Most patients with symptoms had only 1 or 2 symptoms in an ED range, 16%–22% experienced more symptoms (Table 1, Supplement Fig. S1). Further, in 31% (140) of the 444 food challenges, a subjective symptom was reported at more than one dose $\leq$ ED10.

3.3. Symptoms reported in dose ranges $\leq$ ED10

A total of 1092 symptoms were reported for the 444 food challenges $\leq$ ED10, which corresponded to in total 46 unique classified symptoms. At all dose ranges, the vast majority of the symptoms were subjective of nature (Table 1).

In the $\leq$ ED01 range ($n = 109$ symptoms, 68 FC), most reported symptoms were mild subjective or mild objective symptoms (Fig. 2), and mainly (82.6%) symptoms of the oral cavity, eyes and nose, or skin. Most frequently this concerned OAS (37.6%), flush (13.8%) and pruritus of the skin (11%) followed by subjective symptoms such as paresthesia, nausea, abdominal pain/gastric pain (3–5%), or objective symptoms such as erythema, rhinorrhea and red eyes/conjunctivitis (Fig. 3A, and Supplement Fig. S2 for symptoms at the ED ranges). Six (5.5% of 109 symptoms) moderate respiratory symptoms were reported, which were cough ($n = 3$), throat tightness (2), and dyspnea (1), each displayed in a different patient, and different allergens involved.

In the ED01– $\leq$ ED05 range, more symptoms (480 symptoms for 273 food challenges) were reported. Consequently, a larger diversity of symptoms (40 different symptoms) was present, of which 1/3 were reported only once or twice. Again, the majority (76%) were present in the oral cavity, eyes and nose or skin (Fig. 3B, Supplement Fig. S2). Similar symptoms as in the $\leq$ ED01 range were present: OAS (16.7%) and symptoms such as pruritus of oral cavity (11.7%) and paresthesia of the pharynx (10.2%), or symptoms of the skin such as pruritus (8.8%) or flush (11.7%). Gastrointestinal symptoms such as nausea or abdominal pain/gastric pain were present, each approximately 5% of all symptoms at this dose range, usually as a single symptom in the food challenge, though in approximately 1/4 of the cases both symptoms were present in a patient. Symptoms of the respiratory system (5.6% of all symptoms) included objective (cough, 1.0%), and subjective symptoms such as throat tightness (3.3%) and dyspnea (0.8%). Cough was accompanied by other subjective or objective symptoms for individual patients. A large number of other symptoms were reported once to a few times, and mainly were symptoms of the skin or oral cavity.

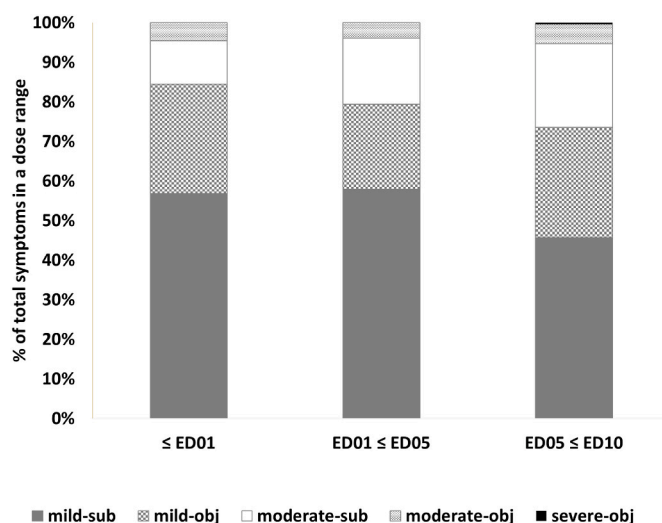


Fig. 2. Nature of all symptoms distributed in the different ED-ranges. Classification of severity of each symptom is provided in Supplement Table S2. Note: the % severe symptoms were very small, i.e. 0.2%, and involved 2 cases, a wheeze and a laryngeal edema in the ED range above the ED05 (ED05– $\leq$ ED10). At doses $\leq$ ED05, no case of severe symptoms were recorded.

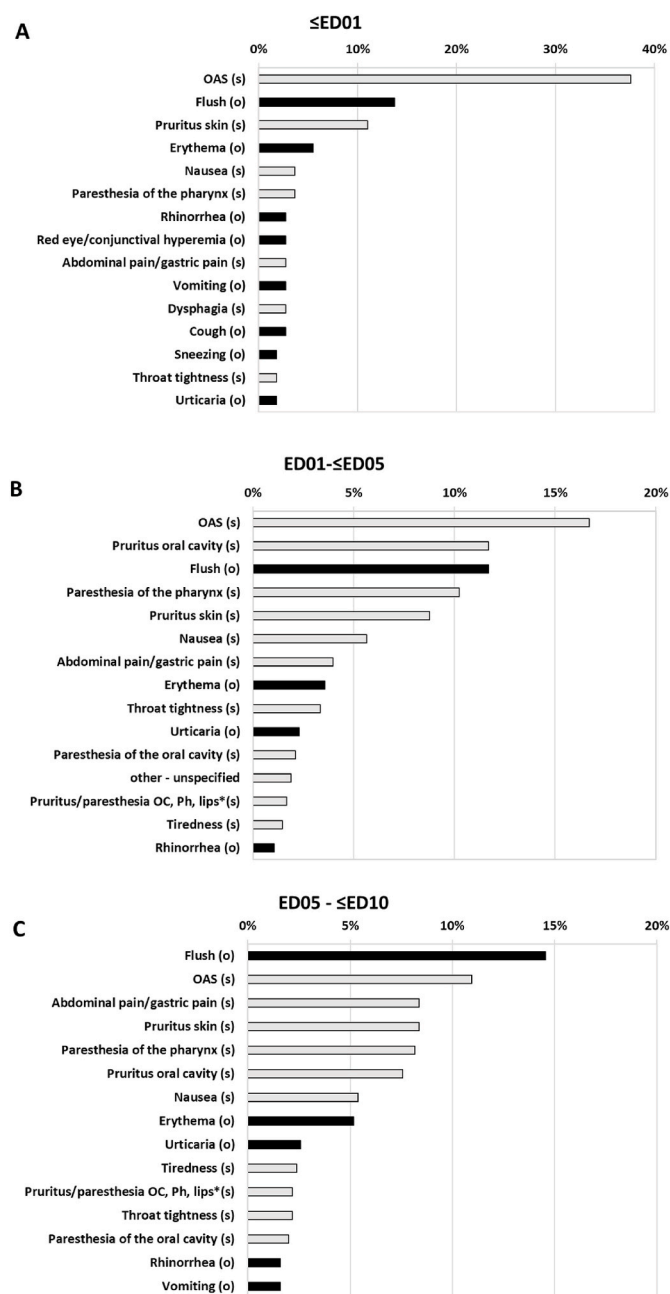


Fig. 3. The occurrence of symptoms in the various dose ranges. The frequency of symptoms reported in a dose range was determined based on the total number of symptoms reported in each dose range (see Table 1). Shown are the top 15 symptoms reported (For the total list of symptoms see Supplement Fig. S2). A) the dose range $\leq$ ED01 ($n = 109$ symptoms; shown here are 97% of all symptoms); B) ED01- $\leq$ ED05 ($n = 480$ symptoms; shown here are 86% of all symptoms) and C) ED05- $\leq$ ED10 of allergens ($n = 503$ symptoms; 83.1% of all symptoms shown). Symptoms were classified as subjective (s) in light grey bars or objective (o) in black bars. *) full description: Pruritus/paresthesia of the oral cavity, pharynx and/or lips (s).

In the range of ED05- $\leq$ ED10 also a large diversity of symptoms ($n = 43$) was reported, that were almost identical to those for the ED01- $\leq$ ED05 range, including the top 15 most reported symptoms (Fig. 3C, Supplement Fig. S2). The majority of these top 15 symptoms were subjective and occurred in the oral cavity, eyes and nose, or skin. Also, the proportion of each of the symptoms was fairly similar and primarily mild to moderate. Two symptoms (0.4% of 503 symptoms) in the ED05- $\leq$ ED10 range were classified as a severe symptom, i.e. a single case of

wheeze, and one case of laryngeal edema.

Overall, the majority of symptoms that patients experienced in the $\leq$ ED10 range were mild (74%–84%) or moderate symptoms (16%–26%), and primarily subjective. Only 0.2% of all symptoms in this range was classified as severe. In the dose ranges $\leq$ ED05, all symptoms were characterized as mild to moderate and no cases of severe symptoms were recorded (Fig. 2).

3.4. Symptoms and allergens

The symptoms most frequently reported were similar for all of the allergenic foods, though with variations in percentages (see heatmap of Supplement Fig. S3) and reflected the general picture of primarily symptoms in the oral cavity, followed by skin symptoms. Except for milk, egg and wheat, for which objective skin symptoms were more prominent. Subjective symptoms were less frequently reported for very young children, and for these 3 allergens, the median age was lower, 2.4 yr (range 0.8–17.6 yr) compared to the median age for other allergenic foods (average of 9.7–39.5 yr) and 7.7 yr (0.8–72.5 yr) for the total group.

3.5. Objective symptoms

For 9.2% of the challenges, the objective LOAEL took place in the dose range $\leq$ ED10, which is close to the 10% that could be expected. The objective symptoms ($n = 347$, 31.9% out of the total symptoms dataset of 1092 symptoms $\leq$ ED10) were primarily mild (78.4%, 77.8–79.2% for the various ED ranges) and the majority concerned skin symptoms (flush followed by erythema and urticaria), accounting for 67.5% of all objective symptoms $\leq$ ED10. Other objective symptoms occurred primarily in the eyes and nose (red eyes, rhinorrhea, sneeze), and oral cavity (lip swelling, oral mucous production) (Fig. 4, and Supplement Table S5). Moderate symptoms (21%, 20–21% for the various ED ranges) were mainly vomiting and cough (generally a mild cough); at doses $\leq$ ED01 all respiratory symptoms were a mild cough, at ED01- $\leq$ ED05 and ED05- $\leq$ ED10 also a few other respiratory symptoms were noted (each once or 2 times); dysphonia, and a wheeze. In the gastrointestinal system vomiting was the most noted objective symptom (approx. 5%), besides diarrhea (<1%). In the ED range above the ED05 (ED05- $\leq$ ED10), 2 cases of a severe symptom were noted, which concerned a wheeze (cashew) and a laryngeal edema (fish) and each occurred at a dose that relates to approximately the ED08.

4. Discussion

Insight into the severity of symptoms at low dose intakes of protein from priority allergenic foods may support decision making and acceptance of harmonized reference doses for Precautionary Allergen Labelling (PAL). The present study investigated all symptoms recorded in the TNO-FARRP threshold database occurring at doses $\leq$ ED10 for the priority allergenic foods for which population threshold dose distributions have been elaborated (Houben et al., 2020; Remington et al., 2020). Our study shows that almost all of the symptoms in the dose range up to the ED10, and all symptoms in the dose range up to an including the ED05, are mild or moderate and mainly concern subjective or objective symptoms of the skin, eyes or nose, or oral cavity. To a lesser extent, gastro-intestinal or respiratory symptoms were reported.

Our database contains 3445 individual threshold datapoints for 14 priority allergenic foods from published and unpublished challenges from clinics worldwide (Remington et al., 2020). The need for a detailed symptom description at every dose was limiting the analysis to a third of all challenges available in the database. The selection was proportionally divided for most allergenic foods, thereby minimizing selection bias for a specific allergenic food. Inherent to the number of data available in the full dataset, more data were present for some allergenic foods, e.g. peanut, hazelnut, egg and milk, than for allergenic foods such as wheat,

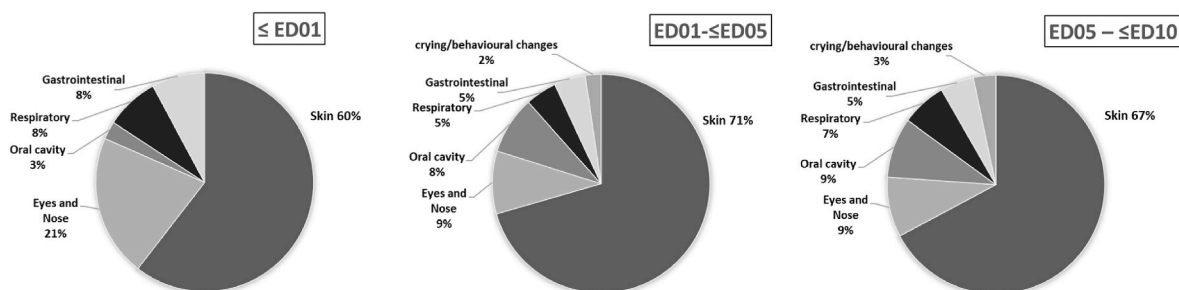


Fig. 4. Objective symptoms distribution per organ system. The frequency of the objective symptoms per organ system in each dose range: for $\leq$ ED01 $n = 38$ objective symptoms, for ED01- $\leq$ ED05 $n = 129$ objective symptoms, and for ED05- $\leq$ ED10 $n = 180$ objective symptoms. Supplement Table S5 provides the percentage grading of objective symptoms reported at the different dose ranges. Grading is based on classification of Table S2.

soy, fish or shrimp that have smaller datasets (Remington et al., 2020). This may have influenced the outcome of our severity analyses. However, if that is the case, our analyses would likely be a worst case analysis, as the dataset contains a relative high portion of peanut data. Turner et al. (2022) found that peanut can be used as a reference allergen for hazard characterization in food allergen risk management, as they found no evidence to suggest that other priority allergens may result in a higher rate of anaphylaxis at low doses of allergen exposure compared with peanut. And, Purington et al. found that at the low dose range there was no evidence for a difference in severity among various allergenic foods including tree nuts, peanut, milk and egg (Purington et al., 2018), suggesting that if differences in numbers of datapoints between various foods could have influenced the outcomes of our analyses, the impact is likely to be limited.

In total a substantial number of challenges (approx. 1100) were available for detailed analysis of the symptoms occurring in the low dose region. The study investigated all symptoms that occurred in ranges based on the cut off values for the ED01, ED05 and ED10 of the cumulative threshold dose distribution of 14 allergenic foods (Houben et al., 2020; Remington et al., 2020). These ED values are generally slightly higher than those based on the discrete threshold dose distributions and thus in theory might include more individuals' symptoms (and potentially more severe symptoms) and thereby represent a worst case choice. The percentage of challenges with an objective LOAEL $\leq$ ED10 (9.2%) is close to the expected 10% and indicates absence of selection bias for the one third of challenges with detailed symptom description. Similar symptoms of primarily skin, oral cavity or eyes and nose were also observed in 2 single dose studies validating the ED05 of peanut (Hourihane et al., 2017) and milk (Turner et al., 2021), supporting the extrapolability of the analyses of symptoms in the low dose ranges for the allergic population.

The main objective of our study was to provide detailed insight into the type of symptoms occurring in the low ED ranges of protein from allergenic foods, the range supporting FAO/WHO recommended Reference Doses (FAO and WHO, 2022). An analysis of symptoms occurring at doses above ED10 of allergenic foods was considered out of scope as well as unreliable. The application of challenge-stopping criteria (or protocol-defined stopping criteria) used in food challenges (Westerhout et al., 2019) would imply that analyses of symptoms at higher dose levels would show a bias towards less severe symptom types. To investigate the symptoms and severity of reactions at high ED values would require a different type of study, e.g. single dose studies as conducted for peanut (Hourihane et al., 2017) and milk (Turner et al., 2021). Applying a severity grading of symptoms supports the interpretation and discussion of the results, but includes a value judgement which is currently not standardized as shown in several overviews (Arasi et al., 2021; Eller et al., 2018; Shah et al., 2023). None of the available grading systems are regarded as the golden standard for classifying symptoms (Arasi et al., 2021; Eller et al., 2018; Zhu et al., 2015),

including recently published multistakeholder approaches to grade severity (Chinthrajah et al., 2022; Dribin et al., 2021; Fernández-Rivas et al., 2021). Further, some of the grading systems require a level of detail that can only be applied for data generated in one particular clinic or a group of clinics (Fernández-Rivas et al., 2021; Purington et al., 2018). Over the years, clinics have applied multiple ways of documenting the reactions in a food challenge and the data in the TNO-FARRP ATDB reflects this; although considerable detail on symptoms is present. For example, intensity (mild or severe cough) or spread of particular symptoms (e.g. localized or generalized urticaria) may have been present in the original patient files but is not consistently reported in publications. For the present study, the symptoms of our dataset were standardized to the list of symptoms that may occur in an allergic reaction defined in cooperation with a large international group of clinicians and scientists (Westerhout et al., 2019). A grading of symptoms into mild, moderate to severe was applied based on the general view present in literature at the time of the analysis (2018–2020), which allows an evaluation of symptom severity at low ED ranges of protein from allergenic foods. It was not our intention to review all available opinions or to develop a new scoring system. The recent systematic overview of published literature and general view for severity presented by (Arasi et al., 2021) did not lead to a need for changing our scaling. However, if future insights would require a different scaling of certain symptoms, the details provided in the present publication are expected to allow independent re-analysis.

Recently, the Ad hoc joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022) recommended health-based guidance values (Reference Doses, RDs) based on population ED05 values for allergenic foods as published by Remington et al. (2020) and Houben et al. (2020). These RDs can be used to calculate action levels for PAL of unintended allergen presence (UAP). Details on how the RDs will support the decision for a PAL are described in (FAO and WHO, 2023). A risk based approach for applying PAL is widely considered as a solution for better informed food choices and improved protection of food allergic consumers (Allen et al., 2014; DunnGalvin et al., 2015; Gupta et al., 2021; Roche et al., 2022). The FAO/WHO recommended RDs were based on the population ED05 values for allergenic foods, but the actual doses were rounded down to levels that for many of the allergenic foods equals to a dose that is between the ED03-ED04 (FAO and WHO, 2022; Houben et al., 2020). This indicates that at exposures up to the RfDs, the vast majority of the allergic population (a predicted 96–97%) will not react with objective symptoms because their individual threshold dose is (considerably) higher. The present analysis illustrated that the type of symptoms in the ranges $\leq$ ED01 or $\leq$ ED05 are very similar in nature. Many patients will not experience any symptom(s) at all, some may experience 1 to 2 subjective symptoms (often itch). Further, those allergic patients with their individual threshold at or below the FAO-WHO recommended RD, would mainly experience mild to moderate subjective symptoms of the oral

cavity, eyes/nose or skin. Moderate objective symptoms were related to urticaria which in the current study was classified rather conservatively compared to the general view that these could be considered mild (Arasi et al., 2021).

In order to define an appropriate level of protection for consumers with food allergies from the risk due to the unintended presence of allergens in food products, an ILSI expert group recently proposed an outline of a framework describing the elements to do this (Madsen et al., 2020). They concluded that sufficient knowledge exists to implement the framework, including sufficient expertise across the whole range of stakeholders to allow opinions to be heard and respected, and a consensus to be achieved. Yet, they emphasized the importance of insight into the nature of symptoms of allergic reactions elicited at dose levels in low ED ranges, to further clarify the level of protection likely conferred by RDs derived from them. The present study provides this detailed insight into the typical subjective and objective symptoms that may occur at low exposure doses as envisaged for the RDs and supports the expected non-severe nature of effects potentially occurring at low frequencies (<5%) at doses not exceeding the RDs. In addition to supporting the safety of the RDs recommended by the FAO/WHO Expert Consultation, the results of our study can be used to support health care workers in their communication to food allergy patients, i.e. in explaining what the RDs mean and what safety level they may expect from RDs when implemented in a food allergen risk management and risk communication system as also proposed by the FAO/WHO Expert Consultation (FAO and WHO, 2023).

Education of stakeholders regarding the interpretation of symptoms in terms of their health impact, seems important as many stakeholders, including patients and health care professionals, often lack sufficient knowledge in this respect (Stockhammer et al., 2020; Turner et al., 2016; Dubois et al., 2018). As indicated before, anaphylaxis often is thought to be a serious life-threatening event, but anaphylaxis is not one single unique allergic symptom, but constitutes a spectrum of symptoms ranging from mild to severe (Cardona et al., 2020; Turner et al., 2019). Anaphylaxis may occur in the food allergic population at doses in the low ED range. The studies of (Patel et al., 2021; Turner et al., 2022) analyzed clinical data (>7500 DBPCFC) and found that up to 5% of the 5% of reactions expected at the ED05 could be classified as anaphylaxis, though none were severe based on the World Allergy Organization definition. In our dataset, at the range $\leq$ ED05, cough was often present as a single symptom, though in a few cases was accompanied by other moderate symptoms of the lower respiratory tract (dysphonia, dyspnea). In the present dataset, three food challenges in the dose range $\leq$ ED05 could be classified as mild anaphylaxis, i.e. WAO grade 3 (Cardona et al., 2020; Turner et al., 2024) (not shown). There were 2 patients that reacted with a severe respiratory symptom (wheeze, laryngeal edema) only in the range ED05 - $\leq$ ED10, at a dose corresponding to approximately the ED08. In addition, the FAO/WHO Expert Consultation recently critically looked at the evidence available and indicated that fatal food anaphylaxis is a very rare event, occurring at less than 1 per 100 000 person years in food-allergic individuals (Umasunthar et al., 2015). Further, the Expert Consultation could not identify any reports on fatal reactions to levels of exposure not exceeding the ED05 for any allergenic food (FAO and WHO, 2022).

In summary, the analysis of the food challenges at the low ED dose ranges for allergenic foods and at FAO/WHO recommended RDs (derived from the ED05) illustrated that the vast majority of all food allergic patients will be without symptoms (i.e. they have a threshold dose that is above the RD), and those sensitive for a dose at or below the ED05 can be expected to experience only mild to moderate symptoms that generally are expected to resolve without medication.

Ethical approval

Ethical approval was not required, as this was a post hoc analysis of anonymized participant data from multiple clinical trials, each of which

had its own individual ethics approval.

CRediT authorship contribution statement

W. Marty Blom: Writing – original draft, Visualization, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Joost Westerhout:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation. **Thuy-My Le:** Writing – review & editing, Methodology, Data curation. **Steve L. Taylor:** Writing – review & editing. **Joseph L. Baumert:** Writing – review & editing, Data curation. **Geert F. Houben:** Writing – review & editing, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgments

This study was executed by the TNO Shared Research Program Food Allergy, a non-profit shared innovation initiative funded by the Food Allergy Research and Resource Program (FARRP) of the University of Nebraska, Nestec, and Dutch Governmental TNO Research Cooperation Funds.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.fct.2025.115250>.

Data availability

The data used for the research is a mixture of publicly available data and confidential data for which the authors do not have permission to share the data

References

- Allen, K.J., Taylor, S.L., 2018. The consequences of precautionary allergen labeling: safe haven or unjustifiable burden? *J. Allergy Clin. Immunol. Pract.* 6, 451–456.e1. <https://doi.org/10.1016/j.jaip.2017.12.025>.
- Allen, K.J., Turner, P.J., Pawankar, R., Taylor, S., Sicherer, S., Lack, G., Rosario, N., Ebisawa, M., Wong, G., Mills, E.N.C., Beyer, K., Fiocchi, A., Sampson, H.A., 2014. Precautionary labelling of foods for allergen content: are we ready for a global framework? *World Allergy Organ. J.* 7, 10. <https://doi.org/10.1186/1939-4551-7-10>.
- Arasi, S., Nurmatov, U., Dunn-Galvin, A., Daher, S., Roberts, G., Turner, P.J., Shinder, S. B., Gupta, R., Eigenmann, P., Nowak-Węgrzyn, A., Sánchez Borges, M.A., Ansotegui, I.J., Fernandez-Rivas, M., Petrou, S., Tanno, L.K., Vazquez-Ortiz, M., Vickery, B.P., Wong, G.W.K., Ebisawa, M., Fiocchi, A., 2021. Consensus on Definition of Food Allergy SEverity (DEFASE) an integrated mixed methods systematic review. *World Allergy Organ. J.* 14. <https://doi.org/10.1016/j.waojou.2020.100503>.
- Ben-Shoshan, M., Harrington, D.W., Soller, L., Fragapane, J., Joseph, L., St Pierre, Y., Godefroy, S.B., Elliot, S.J., Clarke, A.E., 2010. A population-based study on peanut, tree nut, fish, shellfish, and sesame allergy prevalence in Canada. *J. Allergy Clin. Immunol.* 125, 1327–1335. <https://doi.org/10.1016/j.jaci.2010.03.015>.
- Brooke-Taylor, S., Christensen, G., Grinter, K., Sherlock, R., Warren, L., 2018. The allergen bureau VITAL Program. *J. AOAC Int.* 101, 1–6. <https://doi.org/10.5740/jaoacint.17-0392>.
- Cardona, V., Ansotegui, I.J., Ebisawa, M., El-Gamal, Y., Fernandez Rivas, M., Fineman, S., Geller, M., Gonzalez-Estrada, A., Greenberger, P.A., Sanchez Borges, M., Senna, G., Sheikh, A., Tanno, L.K., Thong, B.Y., Turner, P.J., Worm, M., 2020. World allergy organization anaphylaxis guidance 2020. *World Allergy Organ. J.* 13, 100472. <https://doi.org/10.1016/j.waojou.2020.100472>.
- Chinthrajah, R.S., Jones, S.M., Kim, E.H., Sicherer, S.H., Shreffler, W., Lanser, B.J., Atri, N., Babineau, D.C., Adelman, D.C., Iqbal, A., Limb, S.L., Rudman Spengel, A.K., Togias, A., Wood, R.A., 2022. Updating the CoFAR grading scale for systemic allergic

- reactions in food allergy. *J. Allergy Clin. Immunol.* 1–6. <https://doi.org/10.1016/j.jaci.2021.12.789>.
- Cox, L., Larenas-Linnemann, D., Lockey, R.F., Passalacqua, G., 2010. Speaking the same language: the World allergy organization subcutaneous immunotherapy systemic reaction grading system. *J. Allergy Clin. Immunol.* 125. <https://doi.org/10.1016/j.jaci.2009.10.060>.
- Dribin, T.E., Schnadower, D., Spergel, J.M., Campbell, R.L., Shaker, M., Neuman, M.I., Michelson, K.A., Capucilli, P.S., Camargo, C.A., Brousseau, D.C., Rudders, S.A., Assa'ad, A.H., Risma, K.A., Castells, M., Schneider, L.C., Wang, J., Lee, J., Mistry, R. D., Vyles, D., Pistiner, M., Witry, J.K., Zhang, Y., Sampson, H.A., 2021. Severity grading system for acute allergic reactions: a multidisciplinary Delphi study. *J. Allergy Clin. Immunol.* 148, 173–181. <https://doi.org/10.1016/j.jaci.2021.01.003>.
- Dubois, A.E.J., Turner, P.J., Hourihane, J., Ballmer-Weber, B., Beyer, K., Chan, C.-H., Gowland, M.H., O'Hagan, S., Regent, L., Remington, B., Schnadt, S., Stroheker, T., Crevel, R.W.R., 2018. How does dose impact on the severity of food-induced allergic reactions, and can this improve risk assessment for allergenic foods? *Allergy* 1–10. <https://doi.org/10.1111/all.13405>.
- DunnGalvin, A., Chan, C.H., Crevel, R., Grimshaw, K., Poms, R., Schnadt, S., Taylor, S.L., Turner, P., Allen, K.J., Austin, M., Baka, A., Baumert, J.L., Baumgartner, S., Beyer, K., Bucchini, L., Fernández-Rivas, M., Grinter, K., Houben, G.F., Hourihane, J., Kenna, F., Kruizinga, A.G., Lack, G., Madsen, C.B., Clare Mills, E.N., Papadopoulos, N.G., Alldrick, A., Regent, L., Sherlock, R., Wal, J.M., Roberts, G., 2015. Precautionary allergen labelling: perspectives from key stakeholder groups. *Allergy Eur. J. Allergy Clin. Immunol.* 70, 1039–1051. <https://doi.org/10.1111/all.12614>.
- Eller, E., Muraro, A., Dahl, R., Mortz, C.G., Bindslev-Jensen, C., 2018. Assessing severity of anaphylaxis: a data-driven comparison of 23 instruments. *Clin. Transl. Allergy* 8, 1–11. <https://doi.org/10.1186/s13601-018-0215-x>.
- FAO and WHO, 2022. Risk Assessment of Food Allergens. Part 2: review and establish threshold levels in foods for the priority allergens, Risk Assessment of Food Allergens. Part 2: review and establish threshold levels in foods for the priority allergens. <https://doi.org/10.4060/cc2946en>.
- FAO and WHO, 2023. Risk assessment of food allergens – Part 3: review and establish precautionary labelling in foods of the priority allergens, Meeting report. Food Safety and Quality Series No. 16. Rome. <https://doi.org/10.4060/cc6081en>.
- Fernández-Rivas, M., Gómez García, I., Gonzalo-Fernández, A., Ferrer, M.F., Dölle-Bierke, S., Marco-Martin, G., Ballmer-Weber, B.K., Asero, R., Belohlavkova, S., Beyer, K., De Blay, F., Clausen, M., Datema, M.R., Dubakiene, R., Grimshaw, K.E.C., Hoffmann-Sommergruber, K., O'B Hourihane, J., Jedrzejczak-Czechowicz, M., Knulst, A.C., Kralimarkova, T., Le, T.-M., Papadopoulos, N.G., Popov, T.A., Poulsen, L.K., Purohit, A., Senaviratne, S.L., Simpson, A., Sinaniotis, A., Turkalj, M., Vázquez Cortés, S., Vera-Berrios, R.N., Muraro, A., Worm, M., Roberts, G., van Ree, R., Fernandez-Perez, C., Turner, P.J., Mills, E.N.C., 2021. Development and validation of the food allergy severity score. *Allergy* 00, 1–14. <https://doi.org/10.1111/all.15165>.
- Gupta, R., Kanaley, M., Negris, O., Roach, A., Bilaver, L., 2021. Understanding precautionary allergen labeling (PAL) preferences among food allergy stakeholders. *J. Allergy Clin. Immunol. Pract.* 9, 254–264.e1. <https://doi.org/10.1016/j.jaip.2020.09.022>.
- Holleman, B.C., van Os-Medendorp, H., van den Bergh, H., van Dijk, L.M., Linders, Y.F. M., Blom, W.M., Verhoeckx, K.C.M., Michelsen-Huisman, A., Houben, G.F., Knulst, A.C., Lentz, L.R., 2021. Poor understanding of allergen labelling by allergic and non-allergic consumers. *Clin. Exp. Allergy* 51, 1374–1382. <https://doi.org/10.1111/cea.13975>.
- Houben, G.F., Baumert, J.L., Blom, W.M., Kruizinga, A.G., Meima, M.Y., Remington, B. C., Wheeler, M.W., Westerhout, J., Taylor, S.L., 2020. Full range of population Eliciting Dose values for 14 priority allergenic foods and recommendations for use in risk characterization. *Food Chem. Toxicol.* 146, 111831. <https://doi.org/10.1016/j.fct.2020.111831>.
- Hourihane, J.O., Allen, K.J., Shreffler, W.G., DunnGalvin, G., Nordlee, J.A., Zurzolo, G.A., DunnGalvin, A., Gurrin, L.C., Baumert, J.L., Taylor, S.L., 2017. Peanut Allergen Threshold Study (PATS): novel single-dose oral food challenge study to validate eliciting doses in peanut allergic children. *J. Allergy Clin. Immunol.* <https://doi.org/10.1016/j.jaci.2017.01.030>.
- Kimchi, N., Clarke, A., Moisan, J., Lachaine, C., La Vieille, S., Asai, Y., Joseph, L., Mill, C., Ben-Shoshan, M., 2015. Anaphylaxis cases presenting to primary care paramedics in Quebec. *Immun. Inflamm. Dis.* 3, 406–410. <https://doi.org/10.1002/iid3.78>.
- Lange, L., 2014. Quality of life in the setting of anaphylaxis and food allergy. *Allergy J. Int.* 23, 252–260. <https://doi.org/10.1007/s40629-014-0029-x>.
- Madsen, C.B., van den Dungen, M.W., Cochrane, S., Houben, G.F., Knibb, R.C., Knulst, A. C., Ronsmans, S., Yarham, R.A.R., Schnadt, S., Turner, P.J., Baumert, J., Cavandoli, E., Chan, C.H., Warner, A., Crevel, R.W.R., 2020. Can we define a level of protection for allergic consumers that everyone can accept? *Regul. Toxicol. Pharmacol.* 117. <https://doi.org/10.1016/j.yrtph.2020.104751>.
- Michelsen-Huisman, A.D., van Os-Medendorp, H., Blom, W.M., Versluis, A., Castenmiller, J.J.M., Noteborn, H.P.J.M., Kruizinga, A.G., Houben, G.F., Knulst, A. C., 2018. Accidental allergic reactions in food allergy: causes related to products and patient's management. *Allergy* 1–5. <https://doi.org/10.1111/all.13560>.
- Muraro, A., Fernandez-Rivas, M., Beyer, K., Cardona, V., Clark, A., Eller, E., Hourihane, J.O., Jutel, M., Sheikh, A., Agache, I., Allen, K.J., Angier, E., Ballmer-Weber, B., Bilò, M.B., Bindslev-Jensen, C., Camargo Jr, C.A., Cianferoni, A., DunnGalvin, A., Eigenmann, P.A., Halken, S., Hoffmann-Sommergruber, K., Lau, S., Nilsson, C., Poulsen, L.K., Rueff, F., Spergel, J., Sturm, G., Timmermans, F., Torres, M.J., Turner, P., van Ree, R., Wickman, M., Worm, M., Mills, E.N.C., Roberts, G., 2018. The urgent need for a harmonized severity scoring system for acute allergic reactions. *Allergy* 73, 1792–1800. <https://doi.org/10.1111/all.13408>.
- Muraro, A., Roberts, G., Clark, A., Eigenmann, P.A., Halken, S., Lack, G., Moneret-Vautrin, A., Niggemann, B., Rancé, F., 2007. The management of anaphylaxis in childhood: position paper of the European academy of allergology and clinical immunology. *Allergy Eur. J. Allergy Clin. Immunol.* 62, 857–871. <https://doi.org/10.1111/j.1398-9995.2007.01421.x>.
- Patel, N., Adelman, D.C., Anagnostou, K., Baumert, J.L., Blom, W.M., Campbell, D.E., Chinthrajah, R.S., Mills, E.N.C., Javed, B., Purington, N., Remington, B.C., Sampson, H.A., Smith, A.D., Yarham, R.A.R., Turner, P.J., 2021. Using data from food challenges to inform management of consumers with food allergy: a systematic review with individual participant data meta-analysis. *J. Allergy Clin. Immunol.* 147, 2249–2262.e7. <https://doi.org/10.1016/j.jaci.2021.01.025>.
- Purington, N., Chinthrajah, R.S., Long, A., Sindher, S., Andorf, S., O'Laughlin, K., Woch, M.A., Scheiber, A., Assa'ad, A., Pongracic, J., Spergel, J.M., Tam, J., Tilles, S., Wang, J., Galli, S.J., Desai, M., Nadeau, K.C., 2018. Eliciting dose and safety outcomes from a large dataset of standardized multiple food challenges. *Front. Immunol.* 9, 1–11. <https://doi.org/10.3389/fimmu.2018.02057>.
- Remington, B.C., Westerhout, J., Meima, M.Y., Blom, W.M., Kruizinga, A.G., Wheeler, M. W., Taylor, S.L., Houben, G.F., Baumert, J.L., 2020. Updated population minimal eliciting dose distributions for use in risk assessment of 14 priority food allergens. *Food Chem. Toxicol.* 139, 111259. <https://doi.org/10.1016/j.fct.2020.111259>.
- Roche, I., Vale, S.L., Hornung, C.J., Zurzolo, G.A., Netting, M.J., Dharmage, S.C., Gray, C., Lee, N.A., Lacis-Lee, J., Jorgensen, P.F., Smith, J., Freeman, W., Perrett, K. P., Voukelatos, S., McWilliam, V.L., Grinter, K., Koplin, J.J., Said, M., Campbell, D.E., 2022. An international first: stakeholder consensus statement for food allergen management in packaged foods and food service for Australia and New Zealand. *J. Allergy Clin. Immunol. Pract.* 1–10. <https://doi.org/10.1016/j.jaip.2022.03.018>.
- Shah, A., Dribin, T.E., Wang, J., 2023. How to define severity. *Ann. Allergy Asthma Immunol.* 131, 170–175. <https://doi.org/10.1016/j.anaai.2023.05.009>.
- Stockhammer, D., Katelaris, C.H., Simpson, M.D., Vanniasinkam, T., 2020. Perception of food allergy symptom severity differs across stakeholders. *Pediatr. Allergy Immunol.* 31, 321–325. <https://doi.org/10.1111/pai.13178>.
- Taylor, S.L., Baumert, J.L., Kruizinga, A.G., Remington, B.C., Crevel, R.W.R., Brooke-Taylor, S., Allen, K.J., The Allergen Bureau of Australia & New Zealand, Houben, G., 2014. Establishment of reference doses for residues of allergenic foods: report of the VITAL expert panel. *Food Chem. Toxicol.* 63, 9–17. <https://doi.org/10.1016/j.fct.2013.10.032>.
- Turner, P.J., Ansotegui, I.J., Campbell, D.E., Cardona, V., Carr, S., Custovic, A., Durham, S., Ebisawa, M., Geller, M., Gonzalez-Estrada, A., Greenberger, P.A., Hossny, E., Irani, C., Leung, A.S.Y., Levin, M.E., Muraro, A., Oppenheimer, J.J., Ortega Martell, J.A., Pouessel, G., Rial, M.J., Senna, G., Tanno, L.K., Wallace, D.V., Worm, M., Morais-Almeida, M., 2024. Updated grading system for systemic allergic reactions: joint statement of the World allergy organization anaphylaxis committee and allergen immunotherapy committee. *World Allergy Organ. J.* 17, 100876. <https://doi.org/10.1016/j.waojou.2024.100876>.
- Turner, P.J., Baumert, J.L., Beyer, K., Boyle, R.J., Chan, C.-H., Clark, A.T., Crevel, R.W. R., DunnGalvin, A., Fernández-Rivas, M., Gowland, M.H., Grabenhenrich, L., Hardy, S., Houben, G.F., O'B Hourihane, J., Muraro, A., Poulsen, L.K., Pyrz, K., Remington, B.C., Schnadt, S., van Ree, R., Venter, C., Worm, M., Mills, E.N.C., Roberts, G., Ballmer-Weber, B.K., 2016. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy Eur J Allergy Clin Immunol* 72, 9. <https://doi.org/10.1111/all.12924>.
- Turner, P.J., d'Art, Y.M., Duca, B., Castells, S.A., Marco-Martin, G., Vera-Berrios, R.N., Alvarez, O., Bazire, R., Rodríguez del Río, P., Vazquez-Ortiz, M., Baumert, J.L., van Ree, R., Mills, C.E.N., Fernandez-Rivas, M., Hourihane, J.O.B., 2021. Single-dose oral challenges to validate eliciting doses in children with cow's milk allergy. *Pediatr. Allerg. Immunol. (Leipz.)* 32, 1056–1065. <https://doi.org/10.1111/pai.13482>.
- Turner, P.J., Patel, N., Ballmer-Weber, B.K., Baumert, J.L., Blom, W.M., Brooke-Taylor, S., Brough, H., Campbell, D.E., Chen, H., Chinthrajah, R.S., Crevel, R.W.R., Dubois, A.E.J., Ebisawa, M., Elizur, A., Gerds, J.D., Gowland, M.H., Houben, G.F., Hourihane, J.O.B., Knulst, A.C., La Vieille, S., López, M.C., Mills, E.N.C., Polenta, G. A., Purington, N., Said, M., Sampson, H.A., Schnadt, S., Södergren, E., Taylor, S.L., Remington, B.C., 2022. Peanut can Be used as a reference allergen for hazard characterization in food allergen risk management: a rapid evidence assessment and meta-analysis. *J. Allergy Clin. Immunol. Pract.* 10, 59–70. <https://doi.org/10.1016/j.jaip.2021.08.008>.
- Turner, P.J., Worm, M., Ansotegui, I.J., El-Gamal, Y., Rivas, M.F., Fineman, S., Geller, M., Gonzalez-Estrada, A., Greenberger, P.A., Tanno, L.K., Borges, M.S., Senna, G., Sheikh, A., Thong, B.Y., Ebisawa, M., Cardona, V., 2019. Time to revisit the definition and clinical criteria for anaphylaxis? *World Allergy Organ. J.* 12, 100066. <https://doi.org/10.1016/j.waojou.2019.100066>.
- Umasunthar, T., Leonardi-Bee, J., Turner, P.J., Hodes, M., Gore, C., Warner, J.O., Boyle, R.J., 2015. Incidence of food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin. Exp. Allergy* 45, 1621–1636. <https://doi.org/10.1111/cea.12477>.
- Versluis, A., Knulst, A.C., Kruizinga, A.G., Michelsen, A., Houben, G.F., Baumert, J.L., van Os-Medendorp, H., 2015. Frequency, severity and causes of unexpected allergic

- reactions to food: a systematic literature review. *Clin. Exp. Allergy* 45, 347–367. <https://doi.org/10.1111/cea.12328>.
- Warren, C., Jiang, J., Gupta, R., 2020. Epidemiology and burden of food allergy. *Curr. Allergy Asthma Rep.* 20, 6. <https://doi.org/10.1007/s11882-020-0898-7>.
- Westerhout, J., Baumert, J.L., Blom, W.M., Allen, K.J., Ballmer-Weber, B., Crevel, R.W. R., Dubois, A.E.J., Fernández-Rivas, M., Greenhawt, M.J., O'B Hourihane, J., Koplin, J.J., Kruizinga, A.G., Le, T.-M., Sampson, H.A., Shreffler, W.G., Turner, P.J., Taylor, S.L., Houben, G.F., Remington, B.C., 2019. Deriving individual threshold doses from clinical food challenge data for population risk assessment of food allergens. *J. Allergy Clin. Immunol.* <https://doi.org/10.1016/j.jaci.2019.07.046>.
- Zhu, J., Pouillot, R., Kwegyir-Afful, E.K., Luccioli, S., Gendel, S.M., 2015. A retrospective analysis of allergic reaction severities and minimal eliciting doses for peanut, milk, egg, and soy oral food challenges. *Food Chem. Toxicol.* 80, 92–100. <https://doi.org/10.1016/j.fct.2015.02.023>.