

Rostrum

Peanut Can Be Used as a Reference Allergen for Hazard Characterization in Food Allergen Risk Management: A Rapid Evidence Assessment and Meta-Analysis

Paul J. Turner, FRCPCH, PhD^a, Nandinee Patel, MD^a, Barbara K. Ballmer-Weber, MD^{b,c}, Joe L. Baumert, PhD^d, W. Marty Blom, PhD^e, Simon Brooke-Taylor, PhD^f, Helen Brough, MD, PhD^{g,h}, Dianne E. Campbell, MD, PhD^{i,j}, Hongbing Chen, PhD^k, R. Sharon Chinthrajah, MD^l, René W.R. Crevel, PhD^m, Anthony E.J. Dubois, MD, PhDⁿ, Motohiro Ebisawa, MD^o, Arnon Elizur, MD^{p,q}, Jennifer D. Gerdtts, BComm^r, M. Hazel Gowland, PhD^s, Geert F. Houben, PhD^e, Jonathan O.B. Hourihane, DM, FRCPI^t, André C. Knulst, MD, PhD^u, Sébastien La Vieille, MD, MSc^v, María Cristina López, PhD^w, E.N. Clare Mills, PhD^x, Gustavo A. Polenta, PhD^y, Natasha Purington, MS^z, Maria Said, RN^{aa}, Hugh A. Sampson, MD^{i,bb}, Sabine Schnadt, DiplOecTroph^{cc}, Eva Södergren, PhD^{dd,ee}, Stephen L. Taylor, PhD^d, and Benjamin C. Remington, PhD^{d,ff} *London, Bedford, St Albans, Manchester, UK; Zürich, St Gallen, Switzerland; Lincoln, Neb; Utrecht, Groningen, the Netherlands; Milawa, VIC, Westmead, Castle Hill, NSW, Australia; Montrouge, France; Nanchang, China; Stanford, Calif; Sagamihara, Japan; Zerifin, Tel Aviv, Israel; Toronto, Ottawa, ON, Canada; Dublin, Ireland; Buenos Aires, Argentina; New York, NY; Mönchengladbach, Germany; and Uppsala, Sweden*

Regional and national legislation mandates the disclosure of “priority” allergens when present as an ingredient in foods, but this does not extend to the unintended presence of allergens due to shared production facilities. This has resulted in a proliferation of precautionary allergen (“may contain”) labels (PAL) that are frequently ignored by food-allergic consumers. Attempts have been made to improve allergen risk management to better inform the use of PAL, but a lack of consensus has led

to variety of regulatory approaches and nonuniformity in the use of PAL by food businesses. One potential solution would be to establish internationally agreed “reference doses,” below which no PAL would be needed. However, if reference doses are to be used to inform the need for PAL, then it is essential to characterize the hazard associated with these low-level exposures. For peanut, there are now published data relating to over 3000 double-blind, placebo-controlled challenges in allergic

^aNational Heart & Lung Institute, Imperial College London, London, United Kingdom

^bAllergy Unit, Department of Dermatology, University of Zürich, Zürich, Switzerland

^cClinic for Dermatology and Allergology, Kantonsspital St Gallen, St Gallen, Switzerland

^dFood Allergy Research and Resource Program, Department of Food Science and Technology, University of Nebraska, Lincoln, Neb

^eNetherlands Organisation for Applied Scientific Research TNO, Utrecht, the Netherlands

^fBrooke-Taylor & Co Pty Ltd, Milawa, Vic, Australia

^gChildren’s Allergy Service, Evelina Children’s Hospital, Guy’s and St. Thomas’ NHS Foundation Hospital, London, United Kingdom

^hDepartment of Paediatric Allergy, King’s College London, London, United Kingdom

ⁱDepartment of Allergy and Immunology, the Children’s Hospital at Westmead, Westmead, NSW, Australia

^jDBV Technologies, Montrouge, France

^kState Key Laboratory of Food Science and Technology, Sino-German Joint Research Institute, Nanchang University, Nanchang, China

^lSean N. Parker Center for Allergy and Asthma Research, Stanford University School of Medicine, Stanford, Calif

^mRené Crevel Consulting Limited, Bedford, United Kingdom

ⁿGRIAC Research Institute, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands

^oClinical Research Center for Allergy and Rheumatology, National Hospital Organization, Sagamihara National Hospital, Sagamihara, Japan

^pInstitute of Allergy, Immunology and Pediatric Pulmonology, Yitzhak Shamir Medical Center, Zerifin, Israel

^qDepartment of Pediatrics, Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel

^rFood Allergy Canada, Toronto, ON, Canada

^sAllergy Action, St Albans, United Kingdom

^tDepartment of Paediatrics, Royal College of Surgeons in Ireland and Children’s Health Ireland Temple St Hospital, Dublin, Ireland

^uDepartment Dermatology/Allergy and Center for Translational Immunology, University Medical Centre Utrecht, Utrecht University, Utrecht, the Netherlands

^vFood Directorate, Health Canada, Ottawa, ON, Canada

^wFood Engineering Department, San Martín National University, Buenos Aires, Argentina

^xDivision of Infection, Immunity and Respiratory Medicine, Manchester Institute of Biotechnology, University of Manchester, Manchester, United Kingdom

^yInstituto Nacional de Tecnología Agropecuaria (INTA), Instituto Tecnología de Alimentos, Buenos Aires, Argentina

^zDepartment of Medicine, Quantitative Sciences Unit, Stanford University School of Medicine, Stanford, Calif

^{aa}Allergy & Anaphylaxis Australia, Castle Hill, NSW, Australia

^{bb}Division of Pediatric Allergy and Immunology, Icahn School of Medicine at Mount Sinai, New York, NY

^{cc}Deutscher Allergie- und Asthmabund (DAAB), Mönchengladbach, Germany

^{dd}Livsmedelsverket (Swedish Food Agency), Uppsala, Sweden

^{ee}ThermoFisher Scientific, Uppsala, Sweden

^{ff}Remington Consulting Group BV, Utrecht, the Netherlands

This research was funded in part by a UK Medical Research Council Clinician Scientist award to PJT (reference MR/K010468/1). NP and PJT are supported through the NIHR Biomedical Research Centre based at Imperial College Healthcare NHS Trust and Imperial College London. The views expressed in this article are those of the authors and do not necessarily reflect those of the NHS, NIHR, the UK Departments of Health, Livsmedelsverket (Swedish Food Agency) or Health Canada.

Abbreviations used*CI- Confidence interval**DBPCFC- Double-blind, placebo-controlled food challenge**ED- Eliciting dose**ED₀₁- Amount of allergen expected to cause objective symptoms in 1% of the population with that allergy**ED₀₅- Amount of allergen expected to cause objective symptoms in 5% of the population with that allergy**EIA- Exercise-induced anaphylaxis**FAO- Food and Agriculture Organization**FC- Food challenge**PAL- Precautionary allergen labeling**PFAS- Pollen food allergy syndrome**WHO- World Health Organization*

individuals, but a similar level of evidence is lacking for other priority allergens. We present the results of a rapid evidence assessment and meta-analysis for the risk of anaphylaxis to a low-level allergen exposure for priority allergens. On the basis of this analysis, we propose that peanut can and should be considered an exemplar allergen for the hazard characterization at a low-level allergen exposure. © 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>). (*J Allergy Clin Immunol Pract* 2021;■:■-■)

Key words: *Anaphylaxis; Eliciting dose; Food allergy; Precautionary allergen labeling; Reference dose; Threshold*

Conflicts of interest: P. J. Turner reports personal fees from Aimmune Therapeutics, DBV Technologies, Allergenis, UK Food Standards Agency, and ILSI Europe; grants from NIHR/Imperial BRC, UK Medical Research Council, UK Food Standards Agency, End Allergies Together, and Jon Moulton Charity Trust, outside the submitted work. J. L. Baumert reports personal fees from Neogen Corporation, outside the submitted work. W. M. Blom reports grants from the Dutch Governmental TNO Research Cooperation Funds during the conduct of the study. S. Brooke-Taylor reports personal fees from the Allergen Bureau of Australia and New Zealand, outside the submitted work. H. Brough declares speaker fees from DBV Technologies and Sanofi, and research grants from NIH (NAIAD), DBV Technologies, and Aimmune Therapeutics. D. E. Campbell is employed by DBV Technologies, and reports personal fees from Allergenis and Westmead Fertility Centre and grants from National Health and Medical Research Council of Australia, outside the submitted work. R. S. Chinthrajah reports grants from NIAID, CoFAR, Aimmune Therapeutics, DBV Technologies, Astellas, Regeneron, FARE, and Stanford Maternal and Child Health Research Institute (MCHRI); other support from Alladapt Therapeutics, Novartis, Genentech, Sanofi, Allergenis, and Nutricia, outside the submitted work. R. W. R. Crevel reports personal fees from Unilever Pensions, Food Allergy Research and Resource Program (University of Nebraska), Syngenta PLC, Upfield R&D BV, Zoetis LLC, Exponent Ltd, Fermentalg SA, CEV SA, and ILSI-Europe, and other support from EAACI, outside the submitted work. M. Ebisawa reports personal fees from DBV Technologies, Mylan, and ARS Pharmaceuticals, outside the submitted work. J. O. B. Hourihane receives research funding from NCRC Ireland, City of Dublin Skin and Cancer Hospital, Temple St Hospital Foundation, Clemens von Pirquet Foundation, Aimmune Therapeutics, DBV Technologies, and Johnson & Johnson. He is an advisory board member for Aimmune Therapeutics, and receives speaker fees from DBV Technologies. He is a board member of the Irish Association of Allergy and Immunology and the Irish Food Allergy Network, which receive unrestricted grants and logistical support from industry sources for educational activities. E. N. C. Mills reports grants and other support from Reacta Biotech Ltd, grants from the European Food Safety Authority, Food Standards Agency, and other support from the Biotechnology and Biological Sciences Research Council,

In most jurisdictions, regional and national legislation mandates the disclosure of “priority” allergens when present as an ingredient in foods.¹ However, this does not extend to the unintended presence of allergens due to the use of shared production facilities. Attempts to alert consumers of this have contributed to a proliferation of precautionary allergen (“may contain”) labeling (PAL) that poses considerable difficulties to food-allergic consumers, in part because of a lack of transparency in terms of what PAL actually means.² Attempts have been made by industry and regulators to improve allergen risk management to better inform the use of PAL, but to date this has not resulted in a consistent approach; indeed, this is now leading to discordance as some national regulators take different approaches to others.^{1,3} This lack of harmonious approach means that food businesses currently use PAL in different ways.^{2,3}

Currently, there is no global consensus on what levels of allergen exposure cause harm to food-allergic consumers; this is needed to develop a regulatory approach. One strategy has been to establish internationally agreed “reference doses,” below which no PAL would be needed.³⁻⁶ This would provide a regulatory framework for more appropriate and evidence-based use of PAL. Diverse stakeholders including patient representative groups consider that this would result in better informed food choices and thus better protect consumers with food allergy—many of whom currently ignore PAL due to their widespread (and arguably, over-) use and uncertainty in interpretation.^{1,2,7} There is now a significant evidence base to inform population thresholds for eliciting dose (ED), the dose of allergen predicted to provoke reactions in a defined proportion of the food-allergic population. For example, the amount of allergen expected to cause objective symptoms in 5% of the population with that

Medical Research Council, and Innovate UK, outside the submitted work. In addition, Dr Mills has a patent on blinding of allergens in foods for oral food challenges pending, and was a founder director of Reacta Biotech and a member of the board until November 2019; she owns founder shares in the company. M. Said is Chief Executive Officer for Allergy & Anaphylaxis Australia, which reports grants from Bulla Family Dairy, Freedom Foods, Nestle, NSW Food Authority, Mondelez, Nutricia, Abbott, and Sweet William, and nonfinancial support from Nuts for Life, outside the submitted work. H. A. Sampson reports grants from Immune Tolerance Network, NIAID/NIH, personal fees and other support from N-Fold Therapeutics and DBV Technologies, and personal fees from Siolta Therapeutics, outside the submitted work. S. Schnadt is employed by Deutscher Allergie- und Asthmabund e.V. (DAAB), a patient organization which has received industry support. E. Södergren was employed by the Swedish Food Agency (SFA) during the initial drafting of this manuscript, and is now employed by ThermoFisher Scientific. S. L. Taylor reports funding for research and industry outreach activities related to food allergens received from a consortium of more than 100 food processing companies. B. C. Remington reports grants, personal fees, and nonfinancial support from DBV Technologies; nonfinancial support from ILSI Europe, outside the submitted work; and is an adjunct faculty member of the University of Nebraska. The rest of the authors declare that they have no relevant conflicts of interest.

Received for publication July 1, 2021; revised August 3, 2021; accepted for publication August 4, 2021.

Available online ■■

Corresponding author: Paul J. Turner, FRCPCH, PhD, National Heart & Lung Institute, Imperial College London, Norfolk Place, London W2 1PG, United Kingdom. E-mail: p.turner@imperial.ac.uk.

2213-2198

© 2021 The Authors. Published by Elsevier Inc. on behalf of the American Academy of Allergy, Asthma & Immunology. This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>).

<https://doi.org/10.1016/j.jaip.2021.08.008>

allergy (ED_{05}) is a dose predicted to provoke an objective allergic reaction in 5% of the at-risk allergic population.⁶ Such data can and have been used to inform the need for PAL, albeit on a voluntary basis.^{4,5} However, until now, the main consideration has been the proportion of allergic individuals who will have objective symptoms at these levels of exposure, and not necessarily a consideration of how “severe” such symptoms may be. Thus, there is also a need to better characterize the hazard^{8,9} at a given dose—the relationship between a level of allergen exposure (dose) and the nature/severity of any subsequent adverse health outcome—because this relationship is perceived to be of critical importance by allergic consumers and remains the focus of clinical, scientific, and regulatory debate.

Under current European legislation, food may be considered “unsafe” if injurious to health, for example, due to the “particular health sensitivities of a specific category of consumers” such as those with food allergies. However, what constitutes “injurious to health” is not precisely defined; indeed, interpretation of the law indicates that provided a food product is labeled in accordance with legal requirements (ie, including priority allergens where appropriate), food is safe, unless it is specifically marketed for people with those health sensitivities.¹⁰ In Canada, food is also considered to be unsafe if it contains undeclared food allergens, whether as an ingredient or unintended presence due to shared production facilities¹¹; however, the requirement for allergen declaration “does not apply to a food allergen or gluten that is present in a prepackaged product as a result of cross-contamination.”¹² The Food Allergen Labeling and Consumer Protection Act (2004) in the USA more explicitly enshrines the concept of an “allergic response that causes a risk to human health,” which implies that some reactions might not pose such a risk.¹³ By definition, therefore, there is a hierarchy of risks faced by people with food allergy, some of which might not be considered to be a risk to human health.¹⁴ Fatal food anaphylaxis is the most extreme harm that can occur, but fortunately, it is a very rare event, occurring at less than 1 per 100,000 person-years in food-allergic individuals (Figure 1).¹⁵ Investigating fatal reactions is extremely difficult, as it is usually impossible to determine the amount of allergen that has been consumed or the presence of other factors that might have contributed to the fatal outcome (although to date, there are no reports of fatal reactions to levels of exposure not exceeding the ED_{05} for any allergenic food).²⁰ Although fatal reactions can theoretically occur to any allergen, the vast majority of fatal reactions reported in the literature are due to peanut, tree nuts, seafood, and cow’s milk.²¹ Furthermore, such severe reactions are usually due to the consumption of nonprepacked foods (foods from restaurants, bakeries, take-away or fast-food outlets, etc.)^{20,22}; these foods are unlikely to have had a PAL statement in the same way as is the case with prepacked foods. The rarity of fatal reactions and their limited relevance in the context of managing unintended allergen presence makes fatal reactions an inappropriate basis for characterizing the hazard posed by such presence. Furthermore, allergic consumers want more than “just” protection from fatal reactions, given that moderate allergic reactions can be very unpleasant, even if not themselves life-threatening.

If fatal reactions are not appropriate as an outcome for hazard characterization, arguably it is more important to protect the consumer from severe reactions at a population level. However, the assignment of severity for food-induced allergic reactions is inconsistent in the literature, and each method has its

limitations.^{23,24} There is no universally accepted system for scoring the severity of food-allergic reactions. However, most food-allergic consumers and clinicians would consider reactions involving airway/breathing and/or cardiovascular compromise as severe, and there is an international consensus that such symptoms constitute “anaphylaxis” (despite there being multiple definitions for anaphylaxis in the literature).²⁴ Notwithstanding, even nonfatal anaphylaxis is not a single entity in terms of severity (Figure 1). Published data indicate that at least 80% of anaphylaxis reactions are not treated with epinephrine/adrenaline (contrary to international guidelines), but resolve spontaneously.^{16,17} Although nontreatment must not to be condoned, it does demonstrate the spectrum of severity for anaphylaxis, from mild reactions that spontaneously resolve to more severe reactions refractory to initial treatment (occurring in 3.4% [95% confidence interval (CI): 1.9%-5.9%] of treated reactions).¹⁸

If reference doses (such as ED_{05}) are to be used to inform the need for PAL or other risk management options, then it is essential to characterize the hazard associated with these low-level exposures. Assessing the risk of anaphylaxis to a low-dose allergen exposure would therefore seem to be appropriate in terms of this hazard characterization. For example, after an exposure to an ED_{05} amount of peanut (an amount which would, by definition, not cause an objective allergic reaction in 95% of peanut-allergic individuals), one would expect 2.3 episodes of anaphylaxis per 1000 exposures in the peanut-allergic population.¹⁹ At least 80% of these are mild reactions (which, in reality, resolve spontaneously when allergic individuals choose not to follow medical advice and treat), whereas 97% of the remainder would respond to first-line treatment (with epinephrine/adrenaline).¹⁸ In those reporting anaphylaxis to any level of exposure for a food allergen, the risk of fatal outcome is estimated to be $<1:10,000$ ¹⁵; it is likely that this rate would be even lower after an ED_{05} level of exposure. Therefore, the expected rate of fatal reaction to an ED_{05} exposure in an allergic individual can be estimated to be <1 per million (Figure 1). There are currently no reports in the literature of fatal reactions to this level of exposure, for any allergenic food.

For peanut, there are now published data relating to over 3000 double-blind, placebo-controlled challenges in allergic individuals to inform a reference dose and characterize the hazard associated with an ED_{05} exposure.¹⁹ However, for other priority allergens currently defined by the Food and Agriculture Organization/World Health Organization (FAO/WHO) Codex Alimentarius (cereals containing gluten; crustacea, egg, fish, soybean, milk, tree nuts), this level of evidence (both quantity and quality; eg, from double-blind challenges) is lacking, which results in more uncertainty in the estimate of the rate of anaphylaxis to low-level allergen exposures to these allergens. If peanut can be considered a “worst-case” allergen in terms of hazard and risk characterization at low levels of exposure, then this would greatly facilitate attempts to define reference doses and introduce a consistent regulatory framework for the use of PAL acceptable at an international level.

In this rostrum, we propose that “anaphylaxis” can be used as a “marker” for hazard characterization, that is, severity. We present the results of a rapid evidence assessment²⁵ and meta-analysis evaluating the proportion of reactions to a low-dose allergen exposure that result in anaphylaxis for other priority allergens (see this article’s Online Repository at www.jaci-inpractice.org for methodology), to assess the evidence base and evaluate the uncertainty in the evidence (by comparing the 95% CIs for the rate

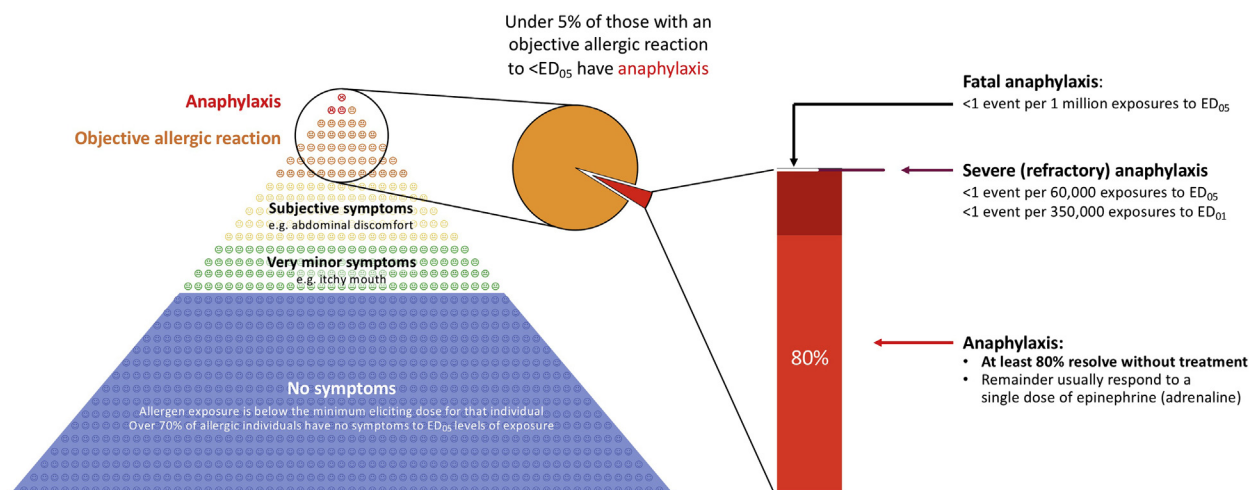


FIGURE 1. Hierarchy of risks faced by people susceptible to IgE-mediated food allergy. Estimates refer to occurrence of allergic symptoms at 15-19

TABLE I. Proportion of peanut-allergic individuals who would be expected to have symptoms after an exposure to an

Peanut	1 mg of protein (\approx upper 95% CI for cumulative <math>ed_{01}< math>)<="" th=""> <th>2.1 mg of protein (= discrete <math>ed_{05}< math>)<="" th=""> <th>7.1 mg of protein (= upper 95% CI for cumulative <math>ed_{05}< math>)<="" th=""> </math>ed_{05}<></th></math>ed_{05}<></th></math>ed_{01}<>	2.1 mg of protein (= discrete <math>ed_{05}< math>)<="" th=""> <th>7.1 mg of protein (= upper 95% CI for cumulative <math>ed_{05}< math>)<="" th=""> </math>ed_{05}<></th></math>ed_{05}<>	7.1 mg of protein (= upper 95% CI for cumulative <math>ed_{05}< math>)<="" th=""> </math>ed_{05}<>
Any symptom (subjective or objective)	14% ²⁷ to 23% ²⁸	20% ²⁷ to 35% ²⁸	35% ²⁷ to 45% ²⁸
Subjective symptoms	13% ²⁷ to 22% ²⁸	15% to 30% ²⁶⁻²⁸	27% ²⁷ to 37% ²⁸
OAS only	5% to 10% ²⁸	5% to 10% ²⁸	5% to 10% ²⁸
Any objective symptom	1%	5%	8% ⁶
Anaphylaxis rate:			
• In those reacting to this dose with objective symptoms	4.2% ¹⁹ (95% CI: 0.7%-22.3%)	4.5% ¹⁹ (95% CI: 1.9%-10.1%)	
• Overall, in the peanut-allergic population	0.04% ¹⁹ (95% CI: 0.01%-0.22%)	0.23% ¹⁹ (95% CI: 0.1%-0.5%)	

CI, Confidence interval;

The cumulative 6 Estimates of the occurrence of different symptoms are based on the literature.²⁶⁻²⁸

of anaphylaxis at low-level exposures for peanut and other priority allergens). We conclude that despite the lower level of evidence—both quantity and quality (eg, not just from a double-blind, placebo-controlled food challenge [DBPCFC])—for allergens other than peanut, there are no data to suggest that other priority allergens cause “more severe” reactions at an

PEANUT

Patel et al¹⁹ recently published a systematic review of over 3000 DBPCFCs to peanut. This analysis found that approximately 4.5% (95% CI: 1.9%-10.1%) of individuals who reacted to ≤ 5 mg of peanut protein and 4.2% (95% CI: 0.7%-22.3%) of individuals who reacted to ≤ 1 mg with objective symptoms experienced anaphylaxis (exposures that approximate to the upper limit of the 95% CI for the amount of allergen expected to

cause objective symptoms in 1% of the population with that allergy [6 A further 3 reports were identified with respect to subjective symptoms experienced after a low-dose peanut exposure at food challenge (FC). In the Peanut Allergen Threshold Study, 378 unselected peanut-allergic children underwent an open, single-dose challenge to 1.5 mg of peanut protein; 67 (17.7%; 95% CI: 14%-22%) developed subjective symptoms.²⁶ Two further series provide dose-distribution curves for any (subjective + objective) symptoms at a DBPCFC to peanut.^{27,28} The latter also reported that at cumulative doses of 0.33 to 3.33 mg of peanut protein, around 5% to 10% of peanut-allergic individuals will experience mild transient oral allergy symptoms.²⁸ At an

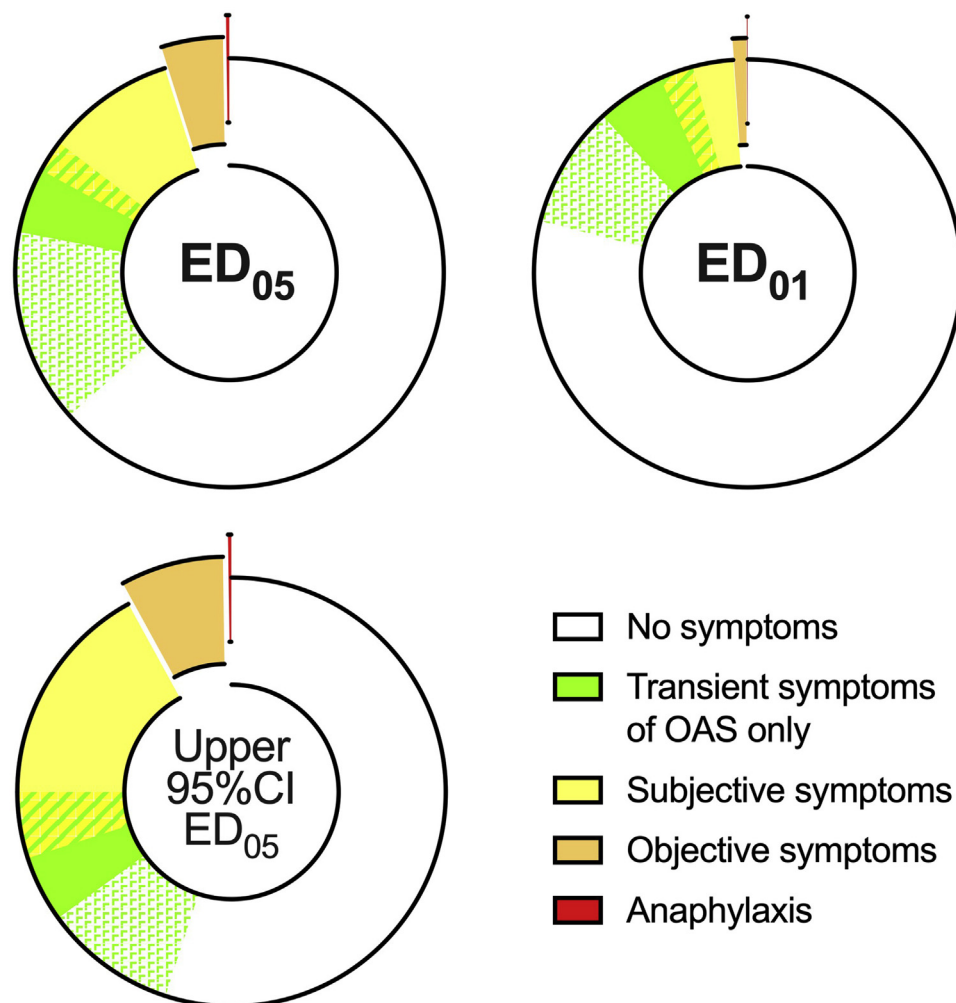


FIGURE 2. Proportion of peanut-allergic individuals expected to have subjective or objective symptoms after an exposure to an ED₀₅ or ED₀₁ amount of peanut. Data from Table I. *CI*, Confidence interval; ED₀₁, amount of allergen expected to cause objective symptoms in 1% of the population with that allergy; ED₀₅, amount of allergen expected to cause objective symptoms in 5% of the population with that allergy; OAS, oral allergy symptoms.

TABLE II. Positive food challenges in the Pronuts study²⁹

	Total positive food challenges (n = 238)	No. reacting to ≤30 mg of protein	Anaphylaxis to ≤30 mg of protein	Symptoms
Almond	6/69 (9%)	0/6		
Brazil	7/100 (7%)	0/7		
Cashew	36/83 (43%)	10/36	0/10	
Hazelnut	30/70 (43%)	6/30	0/6	
Macadamia	16/100 (16%)	3/16	1/3	Laryngeal + lower respiratory symptoms
Pecan	26/92 (28%)	5/26	0/5	
Pistachio	34/94 (36%)	4/34	0/4	
Walnut	36/81 (44%)	7/36	1/7	Pruritic rash, local angioedema, stridor
Peanut	37/66 (56%)	8/37	0/8	

TREE NUTS

Three studies were identified in which nut-allergic patients underwent a formal FC to a range of tree nuts. In the Pronuts

study, a multicenter European study, 122 children (median age, 5.5 years) underwent multiple open FCs to peanut, tree nut, or sesame to assess coexistent allergy.²⁹ A total of 689 FCs to tree

TABLE III. Proportion of positive food challenges (to any dose) associated with symptoms consistent with anaphylaxis in Purington et al³⁰

	No. of positive food challenges	Airway obstruction	Wheezing	Cardiovascular symptoms
Almond	30/44 (68%)	0%	0%	0%
Cashew	151/312 (48%)	1.3%	6.0%	0.7%
Hazelnut	68/95 (72%)	0%	2.9%	0%
Pecan	88/165 (53%)	2.3%	9.1%	0%
Pistachio	60/93 (65%)	1.7%	3.3%	0%
Walnut	121/195 (62%)	0%	2.5%	0%
Peanut	347/795 (44%)	1.2%	8.1%	0.3%

nuts were performed, of which 191 (28%) were positive. Of 35 individuals who reacted to the first challenge dose (≤ 30 mg of protein), only 2 (5.7%) had anaphylaxis (Table II). Purington et al³⁰ undertook a retrospective analysis of 410 individuals (median, 9 years; range, 1-52 years) who underwent DBPCFCs at 7 sites in the USA, which included 512 positive challenges to tree nuts. Severe symptoms were seen at all dosing levels, with no evidence to suggest that rates of anaphylaxis were greater for tree nuts at any level of exposure compared with peanut (Table III). After peanut, cashew and pecan were associated with the highest rates of anaphylaxis.

Further data relating to pecan and cashew can be found in the NutCracker study.³¹ In this study, 83 patients (median age, 8.7 years; range, 3-24 years) were prospectively evaluated for allergy to walnut, pecan, cashew, pistachio, hazelnut, and almond.³¹ Although patients did not undergo a challenge to peanut, rates of lower respiratory symptoms and/or the need for rescue epinephrine due to reactions across the entire FC dosing range were not greater than those reported in the literature for peanut.

Finally, we assessed the rate of anaphylaxis to very low (\leq upper 95th CI for the ED₀₅)⁶ levels of allergen consumption at FC to cashew^{27,29-36} (Table E1, available in this article's Online Repository at www.jaci-inpractice.org), hazelnut^{27-31,37-40} (Table E2, available in this article's Online Repository at www.jaci-inpractice.org), and walnut^{29,30,41-43} (Table E3, available in this article's Online Repository at www.jaci-inpractice.org) reported in the literature, and undertook a meta-analysis (Figures E1-E3, available in this article's Online Repository at www.jaci-inpractice.org). These data are summarized in Table IV. Hazelnut was associated with a higher rate of subjective symptoms at lower doses compared with peanut—something not unexpected, because it is commonly implicated as a cause of pollen food allergy syndrome (PFAS) due to Bet v 1 cross-reactivity with birch pollen.³⁹ This is also consistent with data published by Masthoff et al³⁸ that after a low-dose exposure to hazelnut (≤ 10 mg of protein), subjective symptoms are almost twice as common in adults (in whom PFAS is more common) than in children. Overall, we found no evidence to suggest that tree nut-allergic individuals are more likely to experience anaphylaxis to low levels of exposure to a tree nut, compared with peanut.

SESAME

Sesame is already a priority allergen in the European Union, Canada, Australia, and New Zealand; the FASTER Act was recently passed in the USA, adding sesame to the list of priority

allergens that must be declared when present as an ingredient in foods. Nine published studies were identified for sesame FCs (Table E4, available in this article's Online Repository at www.jaci-inpractice.org), representing 271 positive FCs.^{29,30,44-50} Although some objective reactions were reported to low levels of exposure, only 2 (0.7%) anaphylaxis reactions were reported to < 60 mg level exposures (equivalent to upper 95% CI for ED₀₅ for sesame).⁶ At meta-analysis, this rate was equivalent to that for peanut, with a rate of anaphylaxis to ED₀₅ levels of exposure of 3.0% (95% CI: 0.8%-11%) for sesame (Figure E4, available in this article's Online Repository at www.jaci-inpractice.org).

COW'S MILK

Seventeen studies were identified representing 1045 positive FCs (98% in children) (Table E5, available in this article's Online Repository at www.jaci-inpractice.org).^{27,30,51-65} At meta-analysis, the estimated rate of anaphylaxis in those individuals reacting with objective symptoms to ED₀₅ levels of exposure was 4.9% (95% CI: 2.1%-11%) (Figure E5, available in this article's Online Repository at www.jaci-inpractice.org). Two studies also reported the occurrence of subjective symptoms to low-level exposures. Blom et al²⁷ estimated that 13% to 20% of individuals with an allergy to cow's milk will develop subjective symptoms to ED₀₅ exposures (2.4-6.6 mg of cow's milk protein). Turner et al⁵¹ reported a single-dose challenge study in which 50 of 172 milk-allergic individuals (29%) developed any symptoms to 0.5 mg of cow's milk protein; at least 19% developed transient subjective symptoms, consistent with the estimate of Blom et al.

Although cow's milk allergy is one of the most common food allergies in early childhood, the majority of children tend to outgrow it. This may explain why there is a perception that cow's milk allergy is less "serious" than other food allergies.^{66,67} In reality, there are different phenotypes and children with persisting cow's milk allergy may be more at risk of severe reactions: indeed, cow's milk is the single most common cause of fatal anaphylaxis in children in the United Kingdom⁶⁸ and a common cause of fatal and near-fatal reactions elsewhere.²¹

HEN'S EGG

Twenty studies were identified (Table E6, available in this article's Online Repository at www.jaci-inpractice.org), representing 1180 positive FCs, the vast majority of which (at least 95%) were in children.^{27,30,48,53,58,62,63,69-82} At meta-analysis, the estimated rate of anaphylaxis in those individuals reacting with objective symptoms to ED₀₅ levels of exposure was 1.5% (95% CI: 0.02%-55%) (Figure E6, available in this article's Online Repository at www.jaci-inpractice.org). One study (Blom et al²⁷) also provided an estimate of the occurrence of any symptoms to ED₀₅ levels of exposure of 9% to 14% (which includes both subjective and objective symptoms). Data suggest that egg tends to cause less anaphylaxis (lower respiratory symptoms) and more gastrointestinal symptoms compared with other allergens.⁸³ There are only 2 fatalities to egg reported in the literature,^{21,68,84} despite egg being one of the most common food allergens in preschool children.

WHEAT

IgE-mediated wheat allergy is a relatively uncommon food allergy with a prevalence of under 0.5% in both children and

TABLE IV. Proportion of individuals allergic to cashew, hazelnut, and walnut who would be expected to have symptoms after oral consumption of an ED₀₅ amount

	Cashew		Hazelnut		Walnut	
	0.8 mg 1.6 mg [95% CI: 0.4-9.4 mg]	9.4 mg 32% ²⁷ 20% ²⁷ to 66% ³⁶ Not known	3.5 mg 4.7 mg [95% CI: 1.7-15.7 mg]	15.7 mg 73% ²⁸ to 76% ²⁷ 67% ²⁷ to 70% ²⁸ 20%-30% ²⁸	0.8 mg approx. 8% ²⁷ Not known	13.0 mg approx. 60% ²⁷ approx. 46% ²⁷ Not known
Discrete ED ₀₅	0.8 mg		3.5 mg		0.8 mg	13.0 mg
Cumulative ED ₀₅	1.6 mg [95% CI: 0.4-9.4 mg]		4.7 mg [95% CI: 1.7-15.7 mg]		1.2 mg [95% CI: 0.1-13.0 mg]	
Any symptom (subjective or objective)	8% ²⁷ to >46% ³²	32% ²⁷	31% ²⁷ to 50% ²⁸	73% ²⁸ to 76% ²⁷	approx. 8% ²⁷	approx. 60% ²⁷
Subjective symptoms	3% ²⁷ to 46% ³²	20% ²⁷ to 66% ³⁶	26% ²⁷ to 48% ²⁸	67% ²⁷ to 70% ²⁸	Not known	approx. 46% ²⁷
OAS only	11% ³²	Not known	20%-30% ²⁸		5%	Not known
Any objective symptom (based on ED ₀₅ definition)	5%	12% ⁶	5%	9% ⁵	5%	14% ⁶
Estimated rate of anaphylaxis:						
• In those reacting to ≤ED ₀₅ exposure	4.9% (95% CI: 2.2%-10.5%)		2.5% (95% CI: 0.3%-15.8%)		5.3% (95% CI: 2.0%-13.0%)	
• Overall, in individuals with that specific food allergy	0.25% (95% CI: 0.11%-0.53%)		0.12% (95% CI: 0.02%-0.79%)		(95% CI: 0.10%-0.67%)	
Estimates based on:	597 FCs (318 DBPCFCs, 279 open FCs)		434 FCs (391 DBPCFCs, 43 open FCs)		350 FCs (194 DBPCFCs, 156 open FCs)	

CI, Confidence interval; DBPCFC, double-blind, placebo-controlled food challenge; ED₀₅, amount of allergen expected to cause objective symptoms in 5% of the population with that allergy; FC, food challenge; OAS, oral allergy symptoms.

Estimates of the occurrence of different symptoms are based on the literature.

adults²¹; celiac disease and non-IgE-mediated wheat allergy are more common. However, near-fatal and fatal anaphylaxis have been reported.^{21,85,86} Furthermore, wheat anaphylaxis may be more associated with anaphylactic shock (involving cardiovascular compromise) than other food allergens.⁸⁵ Ten studies were identified, representing 348 positive FCs (at least 90% in children) (Table E7, available in this article's Online Repository at www.jaci-inpractice.org).^{30,53,58,86-92} At meta-analysis, the rate of anaphylaxis in those individuals reacting with objective symptoms to ED₀₅ levels of exposure was estimated to be 2.2% (95% CI: 0.02%-75%) (Figure E7, available in this article's Online Repository at www.jaci-inpractice.org). Wheat is also the most common food allergen implicated in food-dependent, exercise-induced anaphylaxis (EIA).⁸⁵ The available literature suggests that exposure levels causing wheat-dependent EIA in the presence of a relevant cofactor are typically in excess of those triggering reactions in conventional IgE-mediated wheat allergy.^{93,94}

FISH AND SHELLFISH

Threshold data relating to fish and shellfish are limited, in part because of the multiple different species of seafood globally and limited published threshold data across these foods. Moreover, fish and shellfish are reported to have much higher reaction thresholds compared with other food allergens. Despite this, seafood is an emerging and important cause of anaphylaxis, including near-fatal and fatal anaphylaxis globally.²¹ Data from EuroPrevall indicate that around one-third of individuals allergic to seafood would experience subjective symptoms to an ED₀₅ level of exposure of cod or prawn/shrimp.²⁸ We identified 6 studies in the literature, 3 with respect to finned fish (typically cod)^{28,95,96} (Table E8, available in this article's Online Repository at www.jaci-inpractice.org) and 3 evaluating thresholds to prawn/shrimp (Table E9, available in this article's Online Repository at www.jaci-inpractice.org).^{28,97,98} With the paucity of data, no meta-analysis could be performed. The lack of data also results in wide estimated CIs for estimated ED₀₅. Although anaphylaxis has been reported to ED₀₅ levels of exposure, there is no evidence that this occurs more frequently than with peanut; however, the underlying evidence base is far more limited for this food group.

SOYBEAN

The inclusion of soya as a priority allergen in Codex is under review, with a recent recommendation from an FAO/WHO Expert Committee for its removal as a global priority allergen on the basis of a low level of prevalence and low frequency as a cause of anaphylaxis.⁹⁹ For soybean, 5 studies were identified in the literature (Table E10, available in this article's Online Repository at www.jaci-inpractice.org).^{27,58,100-102} Consistent with data suggesting that soybean is an uncommon cause of anaphylaxis globally,²¹ no cases of anaphylaxis to low (<200 mg of protein) levels of exposure were identified.

REPRODUCIBILITY OF THRESHOLDS AND LIKELIHOOD OF ANAPHYLAXIS

Patel et al¹⁹ analyzed data from 534 individuals who underwent at least 2 peanut-DBPCFCs over time, to assess the reproducibility of thresholds and recurrence of anaphylaxis in peanut-allergic individuals. Although the intraindividual variability in ED varied by up to 3-log, in the majority 71.2% (95%

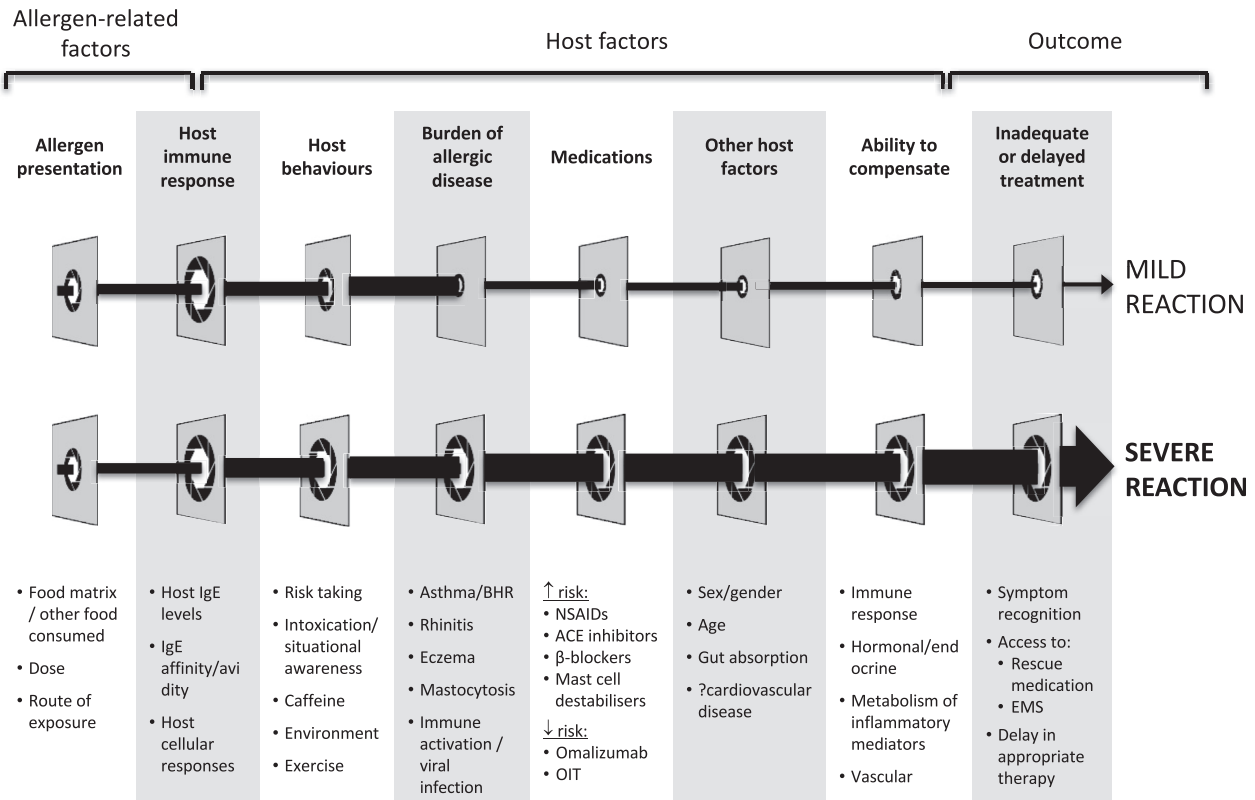


FIGURE 3. Factors that can modulate severity of allergic reactions. Reprinted with permission from Dubois et al.¹⁴ ACE, Angiotensin converting enzyme; BHR, bronchial hyperresponsiveness; EMS, emergency medical services; NSAID, nonsteroidal anti-inflammatory drug; OIT, oral immunotherapy.

CI: 56.2%–82.6%) of individuals, this was limited to a half-log change—equivalent to a single dosing interval when using a PRACTALL-style semilogarithmic dosing regimen.¹⁰³ There was a similar degree of variability in the reproducibility of the dose at which participants experienced anaphylaxis; reassuringly, although some peanut-allergic individuals tolerated an ED₀₅ exposure on one occasion but then reacted on another, no such subject developed anaphylaxis in this cohort. There are very limited data on the reproducibility of clinical thresholds for allergens other than peanut. Limited data ($n \approx 20$) have been published for egg⁶⁹ and wheat,⁸⁷ with no evidence of increased variability in threshold compared with peanut (although for egg, the study was in children exposed to “baked” egg on a regular basis).

Multiple factors can impact on the severity of food-induced allergic reactions, as outlined in Figure 3. These include cofactors or “augmentation” factors such as exercise, stress, medication, sleep deprivation, and alcohol that appear to alter both the threshold at which individuals experience symptoms and the severity of symptoms at any given level of exposure.^{14,104} Importantly, these cofactors are not universal and inconsistently experienced by individuals; in many, if not most individuals, the most well-described factors (exercise, menstruation, alcohol) seem not to impact significantly on reaction severity.¹⁰⁴ In a retrospective survey of almost 500 adults with food allergy, only a small proportion used medication that could influence severity, and under 10% reported exercise or alcohol as a relevant factor in reactions due to inadvertent

exposure.¹⁰⁵ The same study group recently published a prospective evaluation of accidental reactions in 157 patients over a 1-year period. Although 74% of reactions had at least 1 potential cofactor, there was no relationship between the presence of a cofactor and reaction severity.¹⁰⁶

The TRACE peanut study evaluated the impact of significant exercise and sleep deprivation on peanut-induced allergic reactions in 100 peanut-allergic adults, using a randomized study design.¹⁰⁷ On the basis of statistical modeling (rather than raw data), the authors reported a significant impact of both cofactors on reducing clinical thresholds by 45%. However, this decrease—around a $1/2$ -log, equivalent to a single dosing interval when using a PRACTALL-style semilogarithmic dosing regimen—is well within the intraindividual variation in reaction threshold reported by Patel et al.¹⁹ Indeed, in the TRACE study, the factor with the largest impact in threshold variability was the clinical center at which participants were evaluated. Furthermore, exercise was only identified as a significant factor in 1 of the 2 clinical centers.^{107,108} To date, no data relating to reaction severity from the TRACE study have been published. Therefore, although there can be an impact of cofactors on thresholds and severity in some individuals, this does not appear to be any greater than the inherent shift in both clinical thresholds and risk of anaphylaxis identified in the wider food-allergic population, nor does it appear that such effects are predictable. Consumers with food-dependent EIA (predominantly to wheat and possibly seafood) may be an exception: such individuals appear to be tolerant to the allergen in the absence of the relevant cofactor.

TABLE V. Summary table for the rate of anaphylaxis to ED₀₅ levels of exposure in allergic individuals

Allergen	Evidence base (no. of FCs included in dataset)	Discrete ED ₀₅ (mg protein) [95% CI]	Upper limit of the 95% CI for cumulative ED ₀₅ (mg protein)	Expected rate of symptoms to a level of allergen exposure ≤ upper 95% CI for the cumulative ED ₀₅		Expected rate of anaphylaxis to an allergen exposure ≤ upper 95% CI for the cumulative ED ₀₅ , as a proportion of	
				Any symptoms (%)	Objective symptoms (%)	Individuals reacting to ED ₀₅ exposure with objective symptoms	All individuals allergic to this food
Peanut	3151 DBPCFCs	2.1 [1.2-4.6]	7.1	35-45	8	4.5% (95% CI: 1.9%-10%)	2.3 per 1000 (95% CI: 1.0-5.1 per 1000)
Cashew	323 DBPCFCs 421 open FCs	0.8 [0.2-5.0]	9.4	32	12	4.9% (95% CI: 2.2%-10.5%)	2.5 per 1000 (95% CI: 1.1-5.3 per 1000)
Hazelnut	391 DBPCFCs 43 open FCs	3.5 [1.3-12.1]	15.7	approx. 75	9	2.5% (95% CI: 0.3%-15.8%)	1.2 per 1000 (95% CI: 0.2-7.9 per 1000)
Walnut	194 DBPCFCs 156 open FCs	0.8 [0.1-8.9]	13.0	approx. 60	14	5.3% (95% CI: 2.0%-13%)	2.7 per 1000 (95% CI: 1.0-6.7 per 1000)
Sesame	59 DBPCFCs 214 open FCs	2.7 [0.4-34]	58	Not reported	20	3.0% (95% CI: 0.8%-11%)	1.5 per 1000 (95% CI: 0.4-5.7 per 1000)
Cow's Milk	728 DBPCFCs 317 other FCs	2.4 [1.3-5.0]	6.6	20	9	4.9% (95% CI: 2.1%-11%)	2.5 per 1000 (95% CI: 1.1-5.5 per 1000)
Egg	637 DBPCFCs 543 other FCs	2.3 [1.2-4.7]	5.3	14	9	1.5% (95% CI: 0.02%-55%)	0.8 per 1000 (95% CI: 0-27 per 1000)
Wheat	123 DBPCFCs 23 open FCs	6.1 [2.6-15.6]	25	Not reported	11	2.2% (95% CI: 0.02%-75%)	1.1 per 1000 (95% CI: 0-38 per 1000)
Fish	59 DBPCFCs	12.1 [4.5-44]	102	58	25	Insufficient data for meta-analysis	
Shrimp	12 DBPCFCs 46 open FCs	280 [69-880]	1850	57	19	Insufficient data for meta-analysis	
Soya	89 DBPCFCs 51 open FCs	10.0 [2.2-55]	76	Not reported	Not reported	0% (95% CI: 0%-16.8%)	0 per 1000 (95% CI: 0-8.4 per 1000)

CI, Confidence interval; DBPCFC, double-blind, placebo-controlled food challenge; ED₀₅, amount of allergen expected to cause objective symptoms in 5% of the population with that allergy; FC, food challenge.

However, at least for wheat-dependent EIA, EDs for clinical reaction are typically 2 to 3 log greater than ED₀₅ levels of exposure.^{93,94}

SUMMARY AND CONCLUSIONS

There is a consensus that “zero risk” is not realistic or achievable with respect to food allergen risk management.¹⁰⁹ An evidence-based approach to the use of PAL should improve both allergen risk communication to food-allergic consumers and their understanding and application of this information (different outcomes, but of equal importance). However, the reference doses used to inform the use of PAL must be guided by the residual “tolerable risk” and supported by current methods of allergen detection and risk management.

In this rapid evidence assessment and meta-analysis, we found no evidence to suggest that other priority allergens can result in a higher rate of anaphylaxis at low doses of allergen exposure (at around ED₀₅ levels of exposure, which would be expected to cause objective symptoms in 5% of individuals allergic to that specific allergen), compared with peanut (Table V). Furthermore, we did not identify any cases of anaphylaxis at \leq ED₀₅ levels that were refractory to treatment (where administered). Indeed, for many of the reports included in this analysis, a significant proportion of anaphylaxis reactions were not treated with epinephrine/adrenaline (reflecting both local variations in interpretation of anaphylaxis criteria and management of reactions by clinicians). At these low levels of exposure, the probability of anaphylaxis would be expected to be \leq 0.25%. At least 80% of these episodes would resolve without treatment, whereas $>$ 97% of the remainder would respond to first-line treatment (with epinephrine/adrenaline). The risk of a fatal reaction to an ED₀₅ exposure is estimated to be $<$ 1 per million; to date, there are no reports in the literature of fatal reactions to this level of exposure, for any allergenic food.

These data further support the use of ED to inform the need for PAL. Given that the evidence base is strongest for peanut, with data encompassing over 3000 DBPCFCs reported in the literature (including evidence relating to reproducibility of reaction thresholds and the impact of cofactors), we propose that peanut can be used as an exemplar allergen in terms of hazard characterization at ED₀₅ levels of exposure or below. Further work is underway at a global level to consider how reference doses might be used to inform allergen risk management,¹¹⁰ and importantly, how this can be communicated in a reassuring way to consumers with food allergy. Whether the nature of symptoms that are experienced at an ED₀₅ level of exposure are acceptable to stakeholders, including food-allergic consumers, and could be considered to be a “tolerable risk” requires further consensus.

Acknowledgments

We thank the authors of the included studies for their assistance in providing data for this analysis, in particular, Amandine Divaret-Chauveau, Linus Grabenhenrich, Corinne Keet, Lars Lange, Ania Nowak-Wegrzyn, Sarah Saf, and Noriyuki Yanagida.

REFERENCES

- Allen KJ, Turner PJ, Pawankar R, Taylor S, Sicherer S, Lack G, et al. Precautionary labelling of foods for allergen content: Are we ready for a global framework? *World Allergy Organ J* 2014;7:10.

- DunnGalvin A, Chan CH, Crevel R, Grimshaw K, Poms R, Schnadt S, et al. Precautionary allergen labelling: perspectives from key stakeholder groups. *Allergy* 2015;70:1039-51.
- Madsen CB, van den Dungen MW, Cochrane S, Houben GF, Knibb RC, Knulst AC, et al. Can we define a level of protection for allergic consumers that everyone can accept? *Regul Toxicol Pharmacol* 2020;117:104751.
- Taylor SL, Baumert JL, Kruizinga AG, Remington BC, Crevel RW, Brooke-Taylor S, et al. Establishment of reference doses for residues of allergenic foods: report of the VITAL expert panel. *Food Chem Toxicol* 2014;63:9-17.
- Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol* 2014;133:156-64.
- Houben GF, Baumert JL, Blom WM, Kruizinga AG, Meima MY, Remington BC, et al. Full range of population eliciting dose values for 14 priority allergenic foods and recommendations for use in risk characterization. *Food Chem Toxicol* 2020;146:111831.
- Marchisotto MJ, Harada L, Kamdar O, Smith BM, Wasserman S, Sicherer S, et al. Food allergen labeling and purchasing habits in the United States and Canada. *J Allergy Clin Immunol Pract* 2017;5:345-351.e2.
- Food and Agriculture Organization of the United Nations, World Health Organization. Principles and methods for the risk assessment of chemicals in food. Available from: https://apps.who.int/iris/bitstream/handle/10665/44065/WHO_EHC_240_eng.pdf. Accessed June 25, 2021.
- Crevel RW, Baumert JL, Baka A, Houben GF, Knulst AC, Kruizinga AG, et al. Development and evolution of risk assessment for food allergens. *Food Chem Toxicol* 2014;67:262-76.
- Standing Committee on the Food Chain and Animal Health, European Parliament and the Council of the European Union. Guidance on the implementation of articles 11, 12, 14, 17, 18, 19 and 20 of Regulation (EC) N° 178/2002 on general food law. https://ec.europa.eu/food/system/files/2016-10/gf_req_guidance_rev_8_en.pdf. Accessed June 25, 2021.
- Government of Canada. Food and Drugs Act 1985. <https://laws-lois.justice.gc.ca/eng/acts/F-27/>. Accessed June 25, 2021.
- Government of Canada. Food and Drug Regulations. https://laws-lois.justice.gc.ca/eng/regulations/C.R.C.,_c._870/. Accessed June 25, 2021.
- US Food and Drug Administration. Food Allergen Labeling and Consumer Protection Act of 2004. <https://www.fda.gov/food/food-allergens/gluten-free-guidance-documents-regulatory-information/food-allergen-labeling-and-consumer-protection-act-2004-falcpa>. Accessed June 25, 2021.
- Dubois AEJ, Turner PJ, Hourihane J, Ballmer-Weber B, Beyer K, Chan CH, et al. How does dose impact on the severity of food-induced allergic reactions, and can this improve risk assessment for allergenic foods? Report from an ILSI Europe Food Allergy Task Force Expert Group and Workshop. *Allergy* 2018;73:1383-92.
- Umasunthar T, Leonardi-Bee J, Hodes M, Turner PJ, Gore C, Habibi P, et al. Incidence of fatal food anaphylaxis in people with food allergy: a systematic review and meta-analysis. *Clin Exp Allergy* 2013;43:1333-41.
- Noimark L, Wales J, Du Toit G, Pastacaldi C, Haddad D, Gardner J, et al. The use of adrenaline autoinjectors by children and teenagers. *Clin Exp Allergy* 2012;42:284-92.
- Worm M, Moneret-Vautrin A, Scherer K, Lang R, Fernandez-Rivas M, Cardona V, et al. First European data from the network of severe allergic reactions (NORA). *Allergy* 2014;69:1397-404.
- Patel N, Chong KW, Yip AYG, Ierodiakonou D, Bartra J, Boyle RJ, et al. Use of multiple epinephrine doses in anaphylaxis: a systematic review and meta-analysis. *J Allergy Clin Immunol*. <https://doi.org/10.1016/j.jaci.2021.03.042>. Published online April 20, 2021.
- Patel N, Adelman DC, Anagnostou K, Baumert JL, Blom WM, Campbell DE, et al. 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* 2021;147:2249-2262.e7.
- Turner PJ, Jerschow E, Umasunthar T, Lin R, Campbell DE, Boyle RJ. Fatal anaphylaxis: mortality rate and risk factors. *J Allergy Clin Immunol Pract* 2017;5:1169-78.
- Baseggio Conrado A, Patel N, Turner PJ. Global patterns in anaphylaxis due to specific foods: a systematic review. *J Allergy Clin Immunol*. <https://doi.org/10.1016/j.jaci.2021.03.048>. Published online May 1, 2021.
- Turner PJ, Gowland MH, Sharma V, Ierodiakonou D, Harper N, Garcez T, et al. Increase in anaphylaxis-related hospitalizations but no increase in fatalities: an analysis of United Kingdom national anaphylaxis data, 1992-2012. *J Allergy Clin Immunol* 2015;135:956-963.e1.
- Stafford A, Bartra J, Aston A, Mills ENC, Fernandez-Rivas M, Turner PJ. Improving severity scoring of food-induced allergic reactions: a global “best-worst scaling” exercise. *J Allergy Clin Immunol Pract*. <https://doi.org/10.1016/j.jaip.2021.06.056>. Published online July 19, 2021.

24. Stafford A, Patel N, Turner PJ. Anaphylaxis-moving beyond severity.... *J Allergy Clin Immunol* 2021;148:83-5.
25. Collins AM, Coughlin D, Miller J, Kirk S. The production of quick scoping reviews and rapid evidence assessments: a how to guide; 2015. https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/560521/Production_of_quick_scoping_reviews_and_rapid_evidence_assessments.pdf. Accessed June 25, 2021.
26. Hourihane JO, Allen KJ, Shreffler WG, Dunngalvin G, Nordlee JA, Zurzolo GA, et al. Peanut Allergen Threshold Study (PATS): novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *J Allergy Clin Immunol* 2017;139:1583-90.
27. Blom WM, Vlieg-Boerstra BJ, Kruijzinga AG, van der Heide S, Houben GF, Dubois AE. Threshold dose distributions for 5 major allergenic foods in children. *J Allergy Clin Immunol* 2013;131:172-9.
28. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, Defernez M, Sperrin M, Mackie AR, et al. How much is too much? Threshold dose distributions for 5 food allergens. *J Allergy Clin Immunol* 2015;135:964-71.
29. Brough HA, Caubet JC, Mazon A, Haddad D, Bergmann MM, Wassenberg J, et al. Defining challenge-proven coexistent nut and sesame seed allergy: a prospective multicenter European study. *J Allergy Clin Immunol* 2020;145:1231-9.
30. Purington N, Chinthrajah RS, Long A, Sindher S, Andorf S, O'Laughlin K, et al. Eliciting dose and safety outcomes from a large dataset of standardized multiple food challenges. *Front Immunol* 2018;9:2057.
31. Elizur A, Appel MY, Nachshon L, Levy MB, Epstein-Rigbi N, Golobov K, et al. NUT Co Reactivity - ACquiring Knowledge for Elimination Recommendations (NUT CRACKER) study. *Allergy* 2018;73:593-601.
32. McWilliam V, Peters RL, Allen KJ, Dharmage SC, Ponsonby AL, Tang MLK, et al. Skin prick test predictive values for the outcome of cashew challenges in children. *J Allergy Clin Immunol Pract* 2020;8:141-148.e2.
33. Saba L, Clerc-Urmès I, Delahaye C, Chevillot E, Jarlot-Chevaux S, Dumond P, et al. Predictive factors of allergy to pistachio in children allergic to cashew nut. *Pediatr Allergy Immunol* 2020;31:506-14.
34. Sato S, Movérare R, Ohya Y, Ito K, Nagao M, Borres MP, et al. Ana o 3-specific IgE is a predictive marker for cashew oral food challenge failure. *J Allergy Clin Immunol Pract* 2019;7:2909-2911.e4.
35. Lange L, Lasota L, Finger A, Vlajnic D, Büsing S, Meister J, et al. Ana o 3-specific IgE is a good predictor for clinically relevant cashew allergy in children. *Allergy* 2017;72:598-603.
36. van der Valk JP, Gerth van Wijk R, Dubois AE, de Groot H, Reitsma M, Vlieg-Boerstra B, et al. Multicentre double-blind placebo-controlled food challenge study in children sensitised to cashew nut. *PLoS One* 2016;11:e0151055.
37. Moraly T, Pelletier de Chambure D, Verdun S, Preda C, Seynave M, Vilain AC, et al. Oral Immunotherapy for hazelnut allergy: a single-center retrospective study on 100 patients. *J Allergy Clin Immunol Pract* 2020;8:704-709.e4.
38. Masthoff LJN, Blom WM, Rubingh CM, Klemans RJB, Remington BC, Bruijnzeel-Koomen CAFM, et al. Sensitization to Cor a 9 or Cor a 14 has a strong impact on the distribution of thresholds to hazelnut. *J Allergy Clin Immunol Pract* 2018;6:2112-2114.e1.
39. Datema MR, van Ree R, Asero R, Barreales L, Belohlavkova S, de Blay F, et al. Component-resolved diagnosis and beyond: multivariable regression models to predict severity of hazelnut allergy. *Allergy* 2018;73:549-59.
40. Flinterman AE, Hoekstra MO, Meijer Y, van Ree R, Akkerdaas JH, Bruijnzeel-Koomen CA, et al. Clinical reactivity to hazelnut in children: association with sensitization to birch pollen or nuts? *J Allergy Clin Immunol* 2006;118:1186-9.
41. Goldberg MR, Appel MY, Nega R, Levy MB, Epstein-Rigbi N, Nachshon L, et al. A prospective validation of the NUT CRACKER diagnostic algorithm for walnut and pecan allergy with prediction of severity. *J Allergy Clin Immunol Pract* 2021;9:265-274.e6.
42. Remington BC, Westerhout J, Meima MY, Blom WM, Kruijzinga AG, Wheeler MW, et al. Updated population minimal eliciting dose distributions for use in risk assessment of 14 priority food allergens. *Food Chem Toxicol* 2020;139:111259.
43. Blankestijn MA, Remington BC, Houben GF, Baumert JL, Knulst AC, Blom WM, et al. Threshold dose distribution in walnut allergy. *J Allergy Clin Immunol Pract* 2017;5:376-80.
44. Saf S, Sifers TM, Baker MG, Warren CM, Knight C, Bakhl K, et al. Diagnosis of sesame allergy: analysis of current practice and exploration of sesame component Ses i 1. *J Allergy Clin Immunol Pract* 2020;8:1681-1688.e3.
45. Salari F, Bemanian MH, Fallahpour M, Tavakol M, Shokri S, Baniadam L, et al. Comparison of diagnostic tests with oral food challenge in a clinical trial for adult patients with sesame anaphylaxis. *Iran J Allergy Asthma Immunol* 2020;19:27-34.
46. Yanagida N, Ejiri Y, Takeishi D, Sato S, Maruyama N, Takahashi K, et al. Ses i 1-specific IgE and sesame oral food challenge results. *J Allergy Clin Immunol Pract* 2019;7:2084-2086.e4.
47. Appel MY, Nachshon L, Elizur A, Levy MB, Katz Y, Goldberg MR. Evaluation of the basophil activation test and skin prick testing for the diagnosis of sesame food allergy. *Clin Exp Allergy* 2018;48:1025-34.
48. Chan JCK, Peters RL, Koplin JJ, Dharmage SC, Gurrin LC, Wake M, et al. Food challenge and community-reported reaction profiles in food-allergic children aged 1 and 4 years: a population-based study. *J Allergy Clin Immunol Pract* 2017;5:398-409.e3.
49. Dano D, Remington BC, Astier C, Baumert JL, Kruijzinga AG, Bihain BE, et al. Sesame allergy threshold dose distribution. *Food Chem Toxicol* 2015;83:48-53.
50. Leduc V, Moneret-Vautrin DA, Tzen JT, Morisset M, Guerin L, Kanny G. Identification of oleosins as major allergens in sesame seed allergic patients. *Allergy* 2006;61:349-56.
51. Turner PJ, d'Art YM, Duca B, Chastell SA, Marco-Martin G, Vera-Berrios RN, et al. Single-dose oral challenges to validate eliciting doses in children with cow's milk allergy. *Pediatr Allergy Immunol* 2021;32:1056-65.
52. Inuo C, Tanaka K, Nakajima Y, Yamawaki K, Matsubara T, Iwamoto H, et al. Tolerability of partially and extensively hydrolysed milk formulas in children with cow's milk allergy. *Asia Pac J Clin Nutr* 2019;28:49-56.
53. Yanagida N, Sato S, Asaumi T, Ogura K, Ebisawa M. Risk factors for severe reactions during double-blind placebo-controlled food challenges. *Int Arch Allergy Immunol* 2017;172:173-82.
54. Dambacher WM, de Kort EH, Blom WM, Houben GF, de Vries E. Double-blind placebo-controlled food challenges in children with alleged cow's milk allergy: prevention of unnecessary elimination diets and determination of eliciting doses. *Nutr J* 2013;12:22.
55. Lee JH, Kim WS, Kim H, Hahn YS. Increased cow's milk protein-specific IgG4 levels after oral desensitization in 7- to 12-month-old infants. *Ann Allergy Asthma Immunol* 2013;111:523-8.
56. Schoemaker AA, Sprikkelman AB, Grimshaw KE, Roberts G, Grabenhenrich L, Rosenfeld L, et al. Incidence and natural history of challenge-proven cow's milk allergy in European children—EuroPrevall birth cohort. *Allergy* 2015;70:963-72.
57. Keet CA, Frischmeyer-Guerrero PA, Thyagarajan A, Schroeder JT, Hamilton RG, Boden S, et al. The safety and efficacy of sublingual and oral immunotherapy for milk allergy. *J Allergy Clin Immunol* 2012;129:448-455.e5.
58. Rolinck-Werninghaus C, Niggemann B, Grabenhenrich L, Wahn U, Beyer K. Outcome of oral food challenges in children in relation to symptom-eliciting allergen dose and allergen-specific IgE. *Allergy* 2012;67:951-7.
59. Pajno GB, Caminiti L, Ruggeri P, De Luca R, Vita D, La Rosa M, et al. Oral immunotherapy for cow's milk allergy with a weekly up-dosing regimen: a randomized single-blind controlled study. *Ann Allergy Asthma Immunol* 2010;105:376-81.
60. Caminiti L, Passalacqua G, Barberi S, Vita D, Barberio G, De Luca R, et al. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc* 2009;30:443-8.
61. Lam HY, van Hoffen E, Michelsen A, Guikers K, van der Tas CH, Bruijnzeel-Koomen CA, et al. Cow's milk allergy in adults is rare but severe: both casein and whey proteins are involved. *Clin Exp Allergy* 2008;38:995-1002.
62. Morisset M, Moneret-Vautrin DA, Guenard L, Cuny JM, Frentz P, Hatahet R, et al. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur Ann Allergy Clin Immunol* 2007;39:12-9.
63. Patriarca G, Nucera E, Pollastrini E, Roncallo C, De Pasquale T, Lombardo C, et al. Oral specific desensitization in food-allergic children. *Dig Dis Sci* 2007;52:1662-72.
64. Morisset M, Moneret-Vautrin DA, Kanny G, Guénard L, Beaudouin E, Flabbée J, et al. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clin Exp Allergy* 2003;33:1046-51.
65. Baehler P, Chad Z, Gurbindo C, Bonin AP, Bouthillier L, Seidman EG. Distinct patterns of cow's milk allergy in infancy defined by prolonged, two-stage double-blind, placebo-controlled food challenges. *Clin Exp Allergy* 1996;26:254-61.
66. Turner PJ. Persistent allergy to cow's milk: of greater a clinical concern than other food allergies. *Pediatr Allergy Immunol* 2013;24:624-6.

67. Barnett J, Begen FM, Gowland MH, Lucas JS. Comparing the eating out experiences of consumers seeking to avoid different food allergens. *BMC Public Health* 2018;18:1263.
68. Baseggio Conrado A, Ierodiakonou D, Gowland MH, Boyle RJ, Turner PJ. Food anaphylaxis in the United Kingdom: analysis of national data, 1998-2018. *BMJ* 2021;372:n251.
69. Kim EH, Perry TT, Wood RA, Leung DYM, Berin MC, Burks AW, et al. Induction of sustained unresponsiveness after egg oral immunotherapy compared to baked egg therapy in children with egg allergy. *J Allergy Clin Immunol* 2020;146:851-862.e10.
70. Takaoka Y, Maeta A, Takahashi K, Ito Y, Takahashi S, Muroya T, et al. Effectiveness and safety of double-blind, placebo-controlled, low-dose oral immunotherapy with low allergen egg-containing cookies for severe hen's egg allergy: a single-center analysis. *Int Arch Allergy Immunol* 2019;180:244-9.
71. Bellach J, Schwarz V, Ahrens B, Trendelenburg V, Aksünger Ö, Kalb B, et al. Randomized placebo-controlled trial of hen's egg consumption for primary prevention in infants. *J Allergy Clin Immunol* 2017;139:1591-1599.e2.
72. Pérez-Rangel I, Rodríguez Del Río P, Escudero C, Sánchez-García S, Sánchez-Hernández JJ, Ibáñez MD. Efficacy and safety of high-dose rush oral immunotherapy in persistent egg allergic children: a randomized clinical trial. *Ann Allergy Asthma Immunol* 2017;118:356-364.e3.
73. Xepapadaki P, Fiocchi A, Grabenhenrich L, Roberts G, Grimshaw KE, Fiandor A, et al. Incidence and natural history of hen's egg allergy in the first 2 years of life—the EuroPrevall birth cohort study. *Allergy* 2016;71:350-7.
74. Ballmer-Weber BK, Brockow K, Fiocchi A, Theler B, Vogel L, Ring J, et al. Hydrolysed egg displays strong decrease in allergenicity and is well tolerated by egg-allergic patients. *Allergy* 2016;71:728-32.
75. Vazquez-Ortiz M, Alvaro M, Piquer M, Dominguez O, Machinena A, Martín-Mateos MA, et al. Baseline specific IgE levels are useful to predict safety of oral immunotherapy in egg-allergic children. *Clin Exp Allergy* 2014;44:130-41.
76. Turner PJ, Mehr S, Joshi P, Tan J, Wong M, Kakakios A, et al. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. *Pediatr Allergy Immunol* 2013;24:450-5.
77. Dello Iacono I, Tripodi S, Calvani M, Panetta V, Verga MC, Miceli Sopo S. Specific oral tolerance induction with raw hen's egg in children with very severe egg allergy: a randomized controlled trial. *Pediatr Allergy Immunol* 2013;24:66-74.
78. Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S, Galli E. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. *Pediatr Allergy Immunol* 2013;24:75-83.
79. Fernández-Rivas M, Barreales L, Mackie AR, Fritsche P, Vázquez-Cortés S, Jedrzejczak-Czechowicz M, et al. The EuroPrevall outpatient clinic study on food allergy: background and methodology. *Allergy* 2015;70:576-84.
80. Clark A, Islam S, King Y, Deighton J, Szun S, Anagnostou K, et al. A longitudinal study of resolution of allergy to well-cooked and uncooked egg. *Clin Exp Allergy* 2011;41:706-12.
81. Benhamou AH, Zamora SA, Eigenmann PA. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Pediatr Allergy Immunol* 2008;19:173-9.
82. Caffarelli C, Cavagni G, Giordano S, Stapane I, Rossi C. Relationship between oral challenges with previously uningested egg and egg-specific IgE antibodies and skin prick tests in infants with food allergy. *J Allergy Clin Immunol* 1995; 95:1215-20.
83. Gupta M, Grossmann LD, Spergel JM, Cianferoni A. Egg food challenges are associated with more gastrointestinal reactions. *Children (Basel)* 2015;2:371-81.
84. Sampson HA, Mendelson L, Rosen JP. Fatal and near-fatal anaphylactic reactions to food in children and adolescents. *N Engl J Med* 1992;327:380-4.
85. Kraft M, Dölle-Bierke S, Renaudin JM, Rüeff F, Scherer Hofmeier K, Treudler R, et al. Wheat anaphylaxis in adults differs from reactions to other types of food. *J Allergy Clin Immunol Pract* 2021;9:2844-2852.e5.
86. Cianferoni A, Khullar K, Saltzman R, Fiedler J, Garrett JP, Naimi DR, et al. Oral food challenge to wheat: a near-fatal anaphylaxis and review of 93 food challenges in children. *World Allergy Organ J* 2013;6:14.
87. Nowak-Węgrzyn A, Wood RA, Nadeau KC, Pongracic JA, Henning AK, Lindblad RW, et al. Multicenter, randomized, double-blind, placebo-controlled clinical trial of vital wheat gluten oral immunotherapy. *J Allergy Clin Immunol* 2019;143:651-661.e9.
88. Okada Y, Yanagida N, Sato S, Ebisawa M. Better management of wheat allergy using a very low-dose food challenge: a retrospective study. *Allergol Int* 2016;65:82-7.
89. Nilsson N, Sjölander S, Baar A, Berthold M, Pahr S, Vrtala S, et al. Wheat allergy in children evaluated with challenge and IgE antibodies to wheat components. *Pediatr Allergy Immunol* 2015;26:119-25.
90. Christensen MJ, Eller E, Mortz CG, Bindslev-Jensen C. Patterns of suspected wheat-related allergy: a retrospective single-centre case note review in 156 patients. *Clin Transl Allergy* 2014;4:39.
91. Ito K, Futamura M, Borres MP, Takaoka Y, Dahlstrom J, Sakamoto T, et al. IgE antibodies to omega-5 gliadin associate with immediate symptoms on oral wheat challenge in Japanese children. *Allergy* 2008;63:1536-42.
92. Scibilia J, Pastorello EA, Zisa G, Ottolenghi A, Bindslev-Jensen C, Pravettoni V, et al. Wheat allergy: a double-blind, placebo-controlled study in adults. *J Allergy Clin Immunol* 2006;117:433-9.
93. Brockow K, Kneissl D, Valentini L, Zelger O, Grosber M, Kugler C, et al. Using a gluten oral food challenge protocol to improve diagnosis of wheat-dependent exercise-induced anaphylaxis. *J Allergy Clin Immunol* 2015;135: 977-984.e4.
94. Christensen MJ, Eller E, Mortz CG, Brockow K, Bindslev-Jensen C. Exercise lowers threshold and increases severity, but wheat-dependent, exercise-induced anaphylaxis can be elicited at rest. *J Allergy Clin Immunol Pract* 2018; 6:514-20.
95. Sørensen M, Kuehn A, Mills ENC, Costello CA, Ollert M, Småbrekke L, et al. Cross-reactivity in fish allergy: a double-blind, placebo-controlled food-challenge trial. *J Allergy Clin Immunol* 2017;140:1170-2.
96. Helbling A, Haydel R Jr, McCants ML, Musmand JJ, El-Dahr J, Lehrer SB. Fish allergy: is cross-reactivity among fish species relevant? Double-blind placebo-controlled food challenge studies of fish allergic adults. *Ann Allergy Asthma Immunol* 1999;83(Pt 1):517-23.
97. Thalayasingam M, Gerez IF, Yap CG, Llanora GV, Chia IP, Chua L, et al. Clinical and immunochemical profiles of food challenge proven or anaphylactic shrimp allergy in tropical Singapore. *Clin Exp Allergy* 2015;45:687-97.
98. Daul CB, Morgan JE, Hughes J, Lehrer SB. Provocation-challenge studies in shrimp-sensitive individuals. *J Allergy Clin Immunol* 1988;81:1180-6.
99. Food and Agriculture Organization of the United Nations. Ad hoc joint FAO/WHO expert consultation on risk assessment of food allergens—part 1: summary and conclusions of the review and validation of Codex priority allergen list through risk assessment. <http://www.fao.org/3/cb4653en/cb4653en.pdf>. Accessed June 25, 2020.
100. Treudler R, Franke A, Schmiedeknecht A, Ballmer-Weber BK, Worm M, Werfel T, et al. Standardization of double blind placebo controlled food challenge with soy within a multicentre trial. *Clin Transl Allergy* 2016;6:39.
101. Ballmer-Weber BK, Holzhauser T, Scibilia J, Mittag D, Zisa G, Ortolani C, et al. Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. *J Allergy Clin Immunol* 2007;119:1489-96.
102. Zeiger RS, Sampson HA, Bock SA, Burks AW Jr, Harden K, Noone S, et al. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J Pediatr* 1999;134:614-22.
103. Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, et al. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. *J Allergy Clin Immunol* 2012;130:1260-74.
104. Turner PJ, Baumert JL, Beyer K, Boyle RJ, Chan CH, Clark AT, et al. Can we identify patients at risk of life-threatening allergic reactions to food? *Allergy* 2016;71:1241-55.
105. Versluis A, van Os-Medendorp H, Kruizinga AG, Blom WM, Houben GF, Knulst AC. Cofactors in allergic reactions to food: physical exercise and alcohol are the most important. *Immun Inflamm Dis* 2016;4:392-400.
106. Versluis A, van Os-Medendorp H, Blom WM, Michelsen-Huisman AD, Castenmiller JJM, Noteborn HPJM, et al. Potential cofactors in accidental food allergic reactions are frequently present but may not influence severity and occurrence. *Clin Exp Allergy* 2019;49:207-15.
107. Dua S, Ruiz-Garcia M, Bond S, Durham SR, Kimber I, Mills C, et al. Effect of sleep deprivation and exercise on reaction threshold in adults with peanut allergy: a randomized controlled study. *J Allergy Clin Immunol* 2019;144: 1584-1594.e2.
108. Dua S. Peanut allergy: a prospective study of thresholds, co-factors, mediators and severity [doctoral thesis]. Cambridge, United Kingdom: University of Cambridge; 2018.
109. Madsen CB, Hattersley S, Allen KJ, Beyer K, Chan CH, Godefroy SB, et al. Can we define a tolerable level of risk in food allergy? Report from a EuroPrevall/UK Food Standards Agency workshop. *Clin Exp Allergy* 2012;42:30-7.
110. Food and Agriculture Organization of the United Nations and World Health Organization. Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens Part 2: Review and establish threshold levels in foods of the priority allergens. Summary. Available from: https://cdn.who.int/media/docs/default-source/food-safety/jemra/2nd-allergen-summary-report-20aug2021.pdf?sfvrsn=915a8417_8. Accessed August 21, 2021.