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REVIEW ARTICLE

Proposal of 0.5 mg of protein/100 g of processed food as threshold for voluntary declaration of food allergen traces in processed food—A first step in an initiative to better inform patients and avoid fatal allergic reactions: A GA²LEN position paper

Torsten Zuberbier[1] | Tamara Dörr[1] | Werner Aberer[2] | Montserrat Alvaro[3] | Elizabeth Angier[4] | Stefania Arasi[5] | Hasan Arshad[6,7,8] | Barbara Ballmer-Weber[9,10] | Joan Bartra[11,12] | Lisa Beck[13] | Philippe Bégin[14] | Carsten Bindslev-Jensen[15] | Jovanka Bislimovska[16] | Jean Bousquet[1,17,18] | Knut Brockow[19] | Andrew Bush[20] | Antonella Cianferoni[21] | Michael J. Cork[22] | Adnan Custovic[23] | Ulf Darsow[19] | Nicolette de Jong[24] | Diana Deleanu[25] | Stefano Del Giacco[26] | Antoine Deschildre[27,28] | Audrey Dunn Galvin[29,30,31] | Motohiro Ebisawa[32] | Montserrat Fernández-Rivas[33] | Marta Ferrer[34] | Alessandro Fiocchi[5] | Roy Gerth van Wijk[24] | Maia Gotua[35] | Kate Grimshaw[36] | Josefine Grünhagen[1] | Enrico Heffler[37,38] | Michihiro Hide[39] | Karin Hoffmann-Sommergruber[40] | Cristoforo Incorvaia[41] | Christer Janson[42] | Swen Malte John[43,44] | Carla Jones[45] | Marek Jutel[46,47] | Norito Katoh[48] | Benjamin Kendziora[49] | Tamar Kinaciyan[50] | Edward Knol[51,52] | Oksana Kurbacheva[53] | Susanne Lau[54] | Richard Loh[55] | Carlo Lombardi[56] | Mika Mäkelä[57] | Mary Jane Marchisotto[58,59] | Michael Makris[60] | Marcus Maurer[1] | Rosan Meyer[61] | Dragan Mijakoski[16] | Jordan Minov[16] | Joaquim Mullol[62] | Caroline Nilsson[63,64] | Anna Nowak–Wegrzyn[65] | Bright I. Nwaru[66] | Mikela Odemyr[67] | Giovanni Battista Pajno[68] | Sushil Paudel[69] | Nikolaos G. Papadopoulos[70] | Harald Renz[71,72] | Giampaolo Ricci[73] | Johannes Ring[19,74] | Barbara Rogala[75] | Hugh Sampson[76,77,78] | Gianenrico Senna[79] | Brigita Sitkauskiene[80] | Peter Kenneth Smith[81] | Katarina Stevanovic[1] | Sasho Stoleski[16] | Hania Szajewska[82] | Akio Tanaka[83] | Ana Todo-Bom[84] | Fatih Alexander Topal[1] | Erkka Valovirta[85] | Ronald Van Ree[86] | Carina Venter[87] | Stefan Wöhrl[88] | Gary W.K. Wong[89] | Zuotao Zhao[90] | Margitta Worm[1]

[1]Department of Dermatology and Allergy, Charité-Universitätsmedizin Berlin, Humboldt-Uniersität zu Berlin and Berlin Institute of Health, Comprehensive Allergy-Centre, Berlin, Germany

[2]Department of Dermatology, Medical University of Graz, Graz, Austria

[3]Servei Al-lergologia Immunologia Clinica, Hospital Sant Joan de Deu, Barcelona, Spain

[4]Primary Care, Population Science and Medical Education, Faculty of Medicine, University of Southampton, Southampton, UK

[5]Pediatric Allergology Unit, Bambino Gesù Hospital (IRCCS), Rome, Italy

[6]NIHR Southampton Biomedical Research Centre, University Hospital Southampton NHS Foundation Trust, Southampton, UK

[7]Clinical and Experimental Sciences, Faculty of Medicine, University of Southampton, Southampton, UK

[8]The David Hide Asthma and Allergy Research Centre, St Mary's Hospital, Isle of Wight, UK

[9]Department of Dermatology, University Hospital Zürich, Zürich, Switzerland

[10]Clinic for Dermatology and Allergology, Kantonsspital St. Gallen, St. Gallen, Switzerland

[11]Unitat d'Al.lergia, Servei de Neumologia i Al.lergia Respiratoria, Hospital Clinic, Barcelona, Spain

[12]Institut d'Investigacions Biomèdiques August Pi i Sunyer (IDIBAPS), Barcelona, Spain

[13]Department of Dermatology, University of Rochester Medical Center, Rochester, New York, USA

[14]CHU Sainte-Justine, Montréal, Canada

[15]Department of Dermatology and Allergy Center, Odense Research Centre for Anaphylaxis (ORCA), Odense University Hospital Denmark, Odense, Denmark

[16]Faculty of Medicine, Ss. Cyril and Methodius, University in Skopje, Institute of Occupational Health of RNM, WHO Collaborating Center, Skopje, Macedonia

[17]University Hospital Montpellier, Montpellier, France

[18]MACVIA-France, Montpellier, France

[19]Department of Dermatology and Allergy Biederstein, School of Medicine, Technical University of Munich, Munich, Germany

[20]Imperial College and Royal Brompton Hospital, London, UK

[21]Department of Pediatrics, University of Pennsylvania, The Children's Hospital of Philadelphia, Philadelphia, Pennsylvania, USA

[22]University of Sheffield, Sheffield, UK

[23]National Heart and Lung Institute, Imperial College London, London, UK

[24]Section of Allergology and Clinical Immunology, Department of Internal Medicine, Erasmus MC, Rotterdam, The Netherlands

[25]University Medicine and Pharmacy Iuliu Hatieganu, IRGH, Allergy, Cluj-Napoca, Romania

[26]Department of Medical Sciences and Public Health, University of Cagliari, Cagliari, Italy

[27]CHU Lille, Univ Lille, Lille, France

[28]Pediatric Pulmonology and Allergy Unit, Hôpital Jeanne de Flandre, Lille, France

[29]University College Cork, Cork, Ireland

[30]Sechenov University Moscow, Moscow, Russia

[31]Anaphylaxis Ireland, Cork, Ireland

[32]Clinical Research Center for Allergy and Rheumatology, National Hospital Organization Sagamihara National Hospital, Sagamihara, Japan

[33]Allergy Department, Facultad de Medicina, Hospital Clínico San Carlos, Universidad Complutense (UCM), IdISSC, Madrid, Spain

[34]Department of Allergy, Clinica Universidad de Navarra, Pamplona, Spain

[35]Center of Allergy and Immunology, Tbilisi, Georgia

[36]Dietetic Department, Salford Care Organisation, Salford Royal Foundation Trust, Salford, UK

[37]Personalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano (MI), Italy

[38]Department of Biomedical Sciences, Humanitas University, Pieve Emanuele (MI), Italy

[39]Department of Dermatology, Hiroshima Citizens Hospital, Hiroshima, Japan

[40]Department of Pathophysiology and Allergy Research, Medical University of Vienna, Austria

[41]Cardiac/Pulmonary Rehabilitation, ASST Pini/CTO, Milan, Italy

[42]Department of Medical Sciences: Respiratory, Allergy and Sleep Research, Uppsala University, Uppsala, Sweden

[43]Department of Dermatology, Environmental Medicine, Health Theory, University of Osnabrueck, Osnabrueck, Germany

[44]Institute for Interdisciplinary Dermatological Prevention and Rehabilitation (iDerm) at the University of Osnabrueck, Osnabrueck, Germany

[45]Allergy, Kent, UK

[46]Department of Clinical Immunology, Wrocław Medical University, Poland

[47]All-MED Medical Research Institute, Wrocław, Poland

[48]Department of Dermatology, Kyoto Prefectural University of Medicine, Kyoto, Japan

[49]Department of Dermatology and Allergy, University Hospital, LMU Munich, Munich, Germany

[50]Department of Dermatology, Medical University of Vienna, Vienna, Austria

[51]Department of Dermatology and Allergology, University Medical Center Utrecht, Utrecht, The Netherlands

[52]Laboratory of Translational Immunology, University Medical Center Utrecht, Utrecht, The Netherlands

[53]NRC Institute of Immunology FMBA, Moscow, Russia

[54]Pediatric Respiratory Medicine, Immunology and Critical Care Medicine, Charité Universitätsmedizin Berlin, Berlin, Germany

[55]Department of Immunology, Perth Children's Hospital, University of Western Australia, Perth, Western Australia, Australia

[56]Unità Dipartimentale di Allergologia-Immunologia Clinica & Malattie Apparato Respiratorio, Ente Ospedaliero Fondazione Poliambulanza, Brescia, Italy

[57]Skin and Allergy Hospital, Helsinki University Hospital and University of Helsinki, Helsinki, Finland

[58]MJM Advisory, New York, New York, USA

[59]Mary H. Weiser Food Allergy Center, University of Michigan Medicine, Ann Arbor, Michigan, USA

[60]Allergy Unit, 2nd Dpt of Dermatology and Venereology, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece

[61]Department of Paediatrics, Imperial College, London, UK

[62]Rhinology Unit & Smell Clinic, ENT Department, Hospital Clinic, IDIBAPS, Universitat de Barcelona, CIBERES, Barcelona, Catalonia, Spain

[63]Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden

[64]Department of Clinical Science and Education Södersjukhuset, Karolinska Institutet, Stockholm, Sweden

[65]Division of Allergy and Immunology, Department of Pediatrics, Jaffe Food Allergy Institute, Icahn School of Medicine at Mount Sinai, Kravis Children's Hospital, New York, New York, USA

[66]Krefting Research Centre, Institute of Medicine, University of Gothenburg, Gothenburg, Sweden

[67]Asthma and Allergy Association, Stockholm, Sweden

[68]Pediatric unit, Policlinico Hospitsl, University of Messina, Messina, Italy

[69]Civil Service Hospital, Kathmandu, Nepal

[70]Allergy Dpt, 2nd Pediatric Clinic, University of Athens, Athens, Greece

[71]Institute of Laboratory Medicine and Pathobiochemistry, Molecular Diagnostics, Philipps University Marburg University Hospital Giessen and Marburg, Marburg, Germany

[72]Department of Clinical Immunology and Allergology, Laboratory of Immunopathology, Sechenov University, Moscow, Russia

[73]Pediatric Unit, Department of Medical and Surgical Sciences, University of Bologna, Bologna, Italy

[74]Christine Kühne Center for Allergy Research and Education (CK-Care), Davos, Switzerland

[75]Department of Internal Diseases, Allergology & Clinical Immunology Medical, University of Silesia, Katowice, Poland

[76]Elliot and Roslyn Jaffe Food Allergy Institute, New York, New York, USA

[77]Division of Allergy and Immunology, Kravis Children's Hospital, New York, New York, USA

[78]Department of Pediatrics, Icahn School of Medicine at Mount Sinai, New York, New York, USA

[79]Asthma Center and Allergy Unit, Verona University and General Hospital, Verona, Italy

[80]Department of Immunology and Allergology, Lithuanian University of Health Sciences, Kaunas, Lithuania

[81]Griffith University, Southport, Qld, Australia

[82]Department of Paediatrics, The Medical University of Warsaw, Warsaw, Poland

[83]Department of Dermatology, Graduate School of Biomedical and Health Sciences, Hiroshima University, Hiroshima, Japan

[84]Allergy and Clinical Immunology Unit, Centro Hospitalar e Universitário de Coimbra, Coimbra, Portugal

[85]Department of Lung Diseases and Clinical Allergology, University of Turku, and Terveystalo Turku, Allergy Clinic, Turku, Finland

[86]Departments of Experimental Immunology and Otorhinolaryngology, Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands

[87]University of Colorado Denver School of Medicine and Children's Hospital Colorado, Aurora, Colorado, USA

[88]Floridsdorf Allergy Center (FAZ), Vienna, Austria

[89]Department of Paediatrics, The Chinese University of Hong Kong, Hong Kong, Hong Kong

[90]Department of Dermatology, First Hospital, Peking University, Beijing, China

Correspondence
Torsten Zuberbier, Klinik für Dermatologie, Venerologie und Allergologie, Charité - Universitätsmedizin Berlin, Hindenburgdamm 30, Haus II D-12203, Berlin, Germany.
Email: torsten.zuberbier@charite.de

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Abstract

Background: Food anaphylaxis is commonly elicited by unintentional ingestion of foods containing the allergen above the tolerance threshold level of the individual. While labeling the 14 main allergens used as ingredients in food products is mandatory in the EU, there is no legal definition of declaring potential contaminants. Precautionary allergen labeling such as "may contain traces of" is often used. However, this is unsatisfactory for consumers as they get no information if the contamination is below their personal threshold. In discussions with the food industry and technologists, it was suggested to use a voluntary declaration indicating that all declared contaminants are below a threshold of 0.5 mg protein per 100 g of food. This concentration is known to be below the threshold of most patients, and it can be technically guaranteed in most

food production. However, it was also important to assess that in case of accidental ingestion of contaminants below this threshold by highly allergic patients, no fatal anaphylactic reaction could occur. Therefore, we performed a systematic review to assess whether a fatal reaction to 5mg of protein or less has been reported, assuming that a maximum portion size of 1kg of a processed food exceeds any meal and thus gives a sufficient safety margin.

Methods: MEDLINE and EMBASE were searched until 24 January 2021 for provocation studies and case reports in which one of the 14 major food allergens was reported to elicit fatal or life-threatening anaphylactic reactions and assessed if these occurred below the ingestion of 5mg of protein. A Delphi process was performed to obtain an expert consensus on the results.

Results: In the 210 studies included, in our search, no reports of fatal anaphylactic reactions reported below 5 mg protein ingested were identified. However, in provocation studies and case reports, severe reactions below 5 mg were reported for the following allergens: eggs, fish, lupin, milk, nuts, peanuts, soy, and sesame seeds.

Conclusion: Based on the literature studied for this review, it can be stated that cross-contamination of the 14 major food allergens below 0.5 mg/100 g is likely not to endanger most food allergic patients when a standard portion of food is consumed. We propose to use the statement "this product contains the named allergens in the list of ingredients, it may contain traces of other contaminations (to be named, e.g. nut) at concentrations less than 0.5 mg per 100 g of this product" for a voluntary declaration on processed food packages. This level of avoidance of cross-contaminations can be achieved technically for most processed foods, and the statement would be a clear and helpful message to the consumers. However, it is clearly acknowledged that a voluntary declaration is only a first step to a legally binding solution. For this, further research on threshold levels is encouraged.

KEYWORDS
anaphylaxis, food allergy, nutrition

1 | INTRODUCTION

Allergic reactions to foods are a major health problem that has increased in prevalence in recent years and affects 5%–10% of the population in industrialized countries.[1] In children and adolescents, food allergy is common and considerably impacts the quality of life in these patients, as well as their families and caretakers.[2] In this age group, food allergens are also most commonly the cause of anaphylaxis, the most severe form of an allergic reaction. Although fatalities are rare, these reactions to food allergens are potentially life-threatening. Anaphylaxis elicited by food allergens is most commonly reported after unintentional ingestion of foods containing the relevant allergen.

While labeling food products with the 14 main allergens is mandatory in the EU, precautionary allergen labeling such as "may contain," "may contain traces of" or "manufactured in a setting where 'allergen' is processed" is voluntarily placed by food manufacturers. The inconsistent food labeling approaches are met with the uncertainty of consumers, among whose knowledge about the regulations and meaning of this labeling is largely missing.[3] It also has implications for the manufacturers since consumers with a history of severe allergic reactions are less likely to buy food products with the current precautionary allergen label even though other products without precautionary labeling may contain the allergen in the same quantities and the same likelihood as the labeled product.[3]

The implementation of concentrations over which food allergen traces should be declared on the package would therefore be helpful for consumers as well as for manufacturers. The major problem is that the threshold for elicitation of allergic reactions against foods is different in different individuals. The vast majority of food allergic patients have no problems with contaminants and traces of the relevant allergen. For example, most pollen allergic patients with oral food allergy syndrome often only react to the pure cross-reacting food allergens if they are present in amounts above 1000 mg. On the other hand, there are some severely

affected food allergy sufferers, especially to peanuts with thresholds below 1mg. In addition, a true no observed adverse events level (NOAEL), as in cosmetic allergy, is not known for food allergens. In summary, this situation is unsatisfactory: overcautious reporting of potential contamination of allergens creates unnecessary fears in most food allergy sufferers and is not helpful. On the other hand, underreporting of potential contamination is endangering those severely affected by food allergies reacting to minimal amounts.

As this problem is internationally recognized, some national authorities have implemented threshold values over which food allergens have to be labeled on the package. Japanese authorities have decided on a threshold value based on the precision of ELISA test kits.[4] As precision parameters of medical measurement equipment are subject to change, jeopardizing the scientific value of this rule, this approach is met with serious concerns. Switzerland obligates all food producers to list involuntary cross-contaminations above 1 g allergen per 1 kg food product as "may contain traces of …".[5] The German authorities indicate that the threshold depends on the respective allergen.[6] A similar approach is pursued in Australia and New Zealand, where there are no regulations regarding the mandatory declaration of unintentionally present allergens.[7] The VITAL® (Voluntary Incidental Trace Allergen Labelling) program is a joint venture of Australia's leading food manufacturers and the Australian Food and Grocery Council (AFGC). It provides a standardized approach for assessment and declaration of food allergen contamination, recommending thresholds based on scientific data that has been processed in a stacked model averaging program using a range of statistical calculation models.[8] However, this leads to modifying the thresholds for each allergen with every revision of the program. The aim is to protect the "vast majority of people with food allergy" and they state that below the thresholds, only 1% of allergic patients may develop an allergic reaction, this reaction however may be severe.[9,10] The data processed must adhere to high-quality standards and to include only double-blind, placebo-controlled, food challenge studies.[10-12] While this is a very rigorous approach, some issues may cause bias. One is that especially severe allergic reactions are comparatively rare and are often published as case reports or case series only. As this form of study is considered low-quality evidence in medical science, such are not included in the data evaluated by VITAL. Therefore, it is likely that the most severe allergic reactions described in the literature are not included. Also, fatal reactions are not likely to happen while under clinical observation while unintentional ingestion of food allergen out of hospital may be more likely to lead to death and may be reported only in case reports. In this systematic review, an alternative solution for this dilemma is assessed.

Of course, it is acknowledged that some food allergy sufferers who have not undergone placebo-controlled tests may not know their thresholds but still may have a feeling for it based on previous experiences. Therefore, it would be beneficial to know that the allergens included in the food product do not exceed a certain level. However, this food contamination level, or concentration, needs to be low enough to ensure that no life-threatening or fatal reactions have been observed at this level, but also one which can be easily measured with existing technologies in the food industry without increasing the cost of food production. Therefore, in this systematic review, we assess whether a level of 0.5 mg protein/100 g of food of allergenic protein would be less than the lowest published observed adverse effect level (LOAEL) for a fatal reaction. As portion sizes vary, a maximum portion size of 1 kg of processed food was assumed to exceed any meal and thus giving a sufficient safety margin. Therefore, we used 5 mg protein as a threshold in this investigation.

2 | METHODS

This systematic review was conducted according to the PRISMA guidelines for systematic reviews and meta-analyses.[13] The review was registered on PROSPERO as CRD42018110170.

To find an acceptable threshold levels of allergen contamination in processed food that would benefit food allergy sufferers and would be feasible for the food manufacturers, the first talk was conducted on this topic at the BLL meeting of the allergens specialists committee that took place on 8 July 2019 in Berlin, Germany. The conference included representatives of the German food industry, including food technicians and food manufacturers. The main question was which level of food allergen contamination in processed food could be detected analytically and reproducibly in quality management of food production without increasing the price of the food? The level of 5 mg protein was discussed as it is a typical challenge dose in provocation studies. It was also discussed if voluntary labeling would be an option for food production companies. The discussion resulted in the proposal to use the concentration of 0.5 mg of protein per 100 g food as a threshold for voluntary declaration of allergen traces in processed food. In this systematic review, it was deemed mandatory that even if allergy sufferers would not know their personal threshold, that at this level, fatal reactions would have never been observed.

2.1 | Study eligibility

This systematic review includes provocation studies and case reports describing life-threatening anaphylactic reactions to one of the 14 main allergens in food products were reported. Main food allergens were defined in accordance with the European Union's Food Information Regulation No. 1169/2011: crustaceans, cereals containing gluten, eggs, fish, peanuts, soybean, milk, nuts (namely: almond, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia, or Queensland nuts), celery, mustard, sesame seeds, sulfur dioxide and sulfites (sensu stricto and sulfites are not an allergen but known to induce intolerance reactions), lupin, and molluscs (Table 1). Anaphylactic reactions were considered life-threatening in case of a fatal outcome, potentially fatal outcome without intervention (ie, administration of epinephrine, severe dyspnea/asthma, loss of consciousness), positive

TABLE 1 Main food allergens according to the European Union's Food Information Regulation No. 1169/2011

Allergen name	Including	Amount of protein per 100 g of food.
Celery		Celery root 2 g/100 g
Cereals containing gluten	Wheat (such as spelt and khorasan wheat), rye, barley, oats or their hybridized strains, and products thereof	Wheat 12 g/100 g Rye 9 g/100 g Barley 10 g/100 g Oats 12 g/100 g
Crustaceans		Shrimp 19 g/100 g
Eggs		13 g/100 g
Fish		Between 17-20 g/100 g
Lupin		40 g/100 g
Milk		Cow's milk 3 g/100 g
Molluscs		Mussel 11 g/100 g Cuttlefish 16 g/100 g
Mustard		6 g/100 g
Nuts	Almonds, hazelnuts, walnuts, cashews, pecan nuts, Brazil nuts, pistachio nuts, macadamia or Queensland nuts, and products thereof	Almond 19 g/100 g Brazil nut 14 g/100 g Cashew 18 g/100 g Hazelnut 12 g/100 g Macadamia 9 g/100 g Pecan nut 11 g/100 g Pistachio 18 g/100 g Walnut 14 g/100 g
Peanut		25 g/100 g
Sesame seeds		21 g/100 g
Soybeans		Soybeans 38 g/100 g Soydrink 4 g/100 ml
Sulfur dioxide and sulfites	At concentrations of more than 10 mg/kg or 10 mg/L in terms of the total SO2 Sulfites are not an allergen but known to induce intolerance reactions	Not applicable

shock index, and/or hypotension, and/or heart failure. Included studies and case reports had to give information on the approximate amount of ingested food, for example, "one bite." Publications had to be written in English. Animal studies were excluded.

There is also an abundance of scientific literature that is written in Spanish, French, German, and Japanese language for which quoted reviews in English exist.

2.2 | Search strategy and literature screening

MEDLINE and EMBASE electronic databases were searched via Ovid from their inception until January 2021. The exact search terms are presented in Appendix 1. Titles and abstracts of the retrieved references were screened by a team of three reviewers, duplicates were eliminated, and potentially relevant references were identified. A full-text review of the remaining references was performed. Studies in which relevance was unclear were discussed by the team of reviewers. In addition, the bibliographies of included studies and case reports revealed by the search strategy were searched for eligible articles missed by the search strategy.

2.3 | Data extraction and analysis

Data regarding the type of ingested food, the approximately ingested amount of food, and the type of life-threatening anaphylactic reaction were extracted onto a predefined datasheet by the three reviewers. In addition, we searched and noted the usual concentration of allergenic protein for every food product used in the included provocation studies or described in the included case studies and calculated the amount of ingested allergenic protein. This process was verified by a registered dietitian. The studies were analyzed regarding the occurrence of life-threatening reactions and the reported amount of food protein provoking the reaction. Finally, the data were presented in a table and summarized narratively.

2.4 | Inclusion of authors and discussion with stakeholders

An open call for participation was made within the GA²LEN network, which includes EAACI and EFA as members. In addition, further patient organizations and other experts in the field of allergology and immunology were actively approached. Some non-GA²LEN members accepted the invitation. Participation was denied either due to a lack of time or stating a conflict of interest. A Delphi process was performed which included all participants. A consensus was obtained after two rounds of expert panel evaluations that took place on 10 October 2020 and 10 June 2021. The expert panel consisted of German patient organizations, the members of the CODEX alimentarius working group, food industry legal advisors, and food technologists. Additional data provided by the panel members were evaluated and included if eligibility of the study was given.

2.5 | Risk of bias

The approach that was used in this systematic review has a high level of evidence to suggest that at the concentration of 0.5 mg/100 g limited to no food fatal reactions will occur; however, there is a lower level of evidence regarding the no observed level threshold in severely affected allergy sufferers. This is based on the search string which will not find these provocation tests in which no life-threatening symptoms have occurred.

3 | RESULTS

The search in MEDLINE and EMBASE via Ovid yielded 3289 references, of which we included 90 provocation studies and 88 case studies. Figure 1 gives the PRISMA flowchart that presents an overview of the search results and study selection.

We analyzed double-blind, placebo-controlled provocation tests and case report different minimal threshold levels for different allergens. Some of the other 14 allergens, which must be declared in the European Union, such as mustard and molluscs, have not been reported as being the trigger of a severe allergic reactions at very low levels. Table 2 summarizes the findings from all studies included in this analysis that reported severe allergic reactions after ingestion of less than 5 mg allergen protein or where the ingested amount was unclear. In addition, a summary with all provocation studies and case reports included in this analysis is found in the Tables S1 and S2.

In a cohort of food allergic children used by Moneret-Vautrin et al.[23] for the evaluation of personalized care projects, 2 asthmatic reactions resulting from peanut protein amount lower than 5 mg have been described. However, the authors state in their paper that no fatal reactions were observed. One anaphylactic shock was observed in this study which occurred after ingestion of 965 mg peanut, which amounts to more than 240 mg protein.

Ebrahimi et al.[29] report respiratory distress after 3 drops of milk-based formula in one study subject who needed to be treated with epinephrine. They used BioMeal, Fassbel, Belgium, a formula which is no longer available. According to the EU regulations, infant

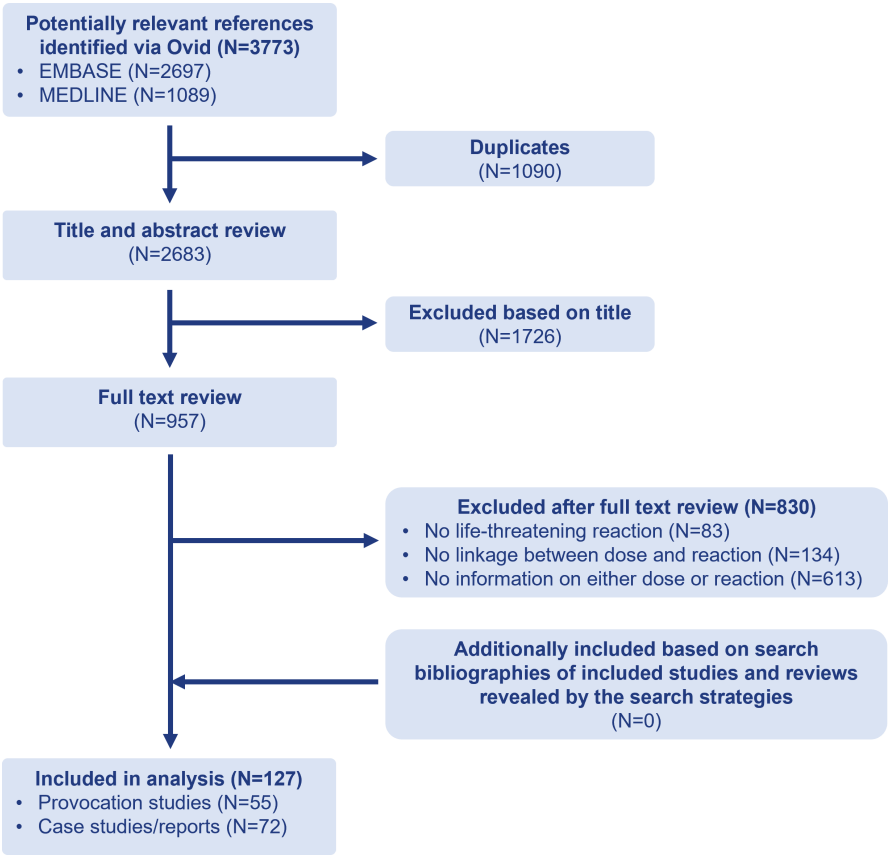

FIGURE 1 Search results and selection of studies

TABLE 2 Summary of data from provocation studies and case reports in which ingestion of less than 5 mg of allergen protein elicited a severe allergic reaction

Allergen	Food product	Nature of life-threatening allergic reaction	No. of participants (no. experiencing a severe reaction)[a]	Amount of food that provoked a severe reaction	Amount of allergen protein (mg) that provoked a severe reaction	Study
Cereals	No report found for reactions at or below 5 mg					
Celery	No report found for reactions at or below 5 mg					
Crustacean	No report found for reactions at or below 5 mg					
Egg	Mortadella	abdominal pain, throat itching, vomit, dyspnea	1(1)	Mortadella 25 mg	0.0503	Tripodi et al. 2009[14]
Fish	Fish	Asthma or mild anaphylaxis	1(1)	Fish 8 mg	1.36	Lefevre et al. 2016[15]
Lupin	Short crust pastry containing lupin flour as minor ingredient	asthma	2(1)	Small amount	Not determinable	Bansal et al. 2014[16]
Milk	Cow's Milk	Asthma or mild anaphylaxis	5	CM <0,05 mg	0.0015	Lefevre et al. 2016[15]
Milk	Cow's milk	Systemic symptoms		Even traces	Not determinable	Poza-Guedes et al. 2014[17]
Milk	Cow's milk		10(?)	Trace amounts	Not determinable	Paiva et al. 2009[18]
Milk	Cow's milk	Syncope, hypoxia, and drop in blood pressure treated with epinephrine	1(1)	Accidental ingestion of trace amounts	Not determinable	Lisann et al. 2014[19]
Milk	Cow's milk	Syncope, hypoxia, and drop in blood pressure treated with epinephrine	1(1)	Accidental ingestion of trace amounts	Not determinable	Lisann et al. 2014[19]
Molluscs	No report found for reactions at or below 5 mg					
Mustard	No report found for reactions at or below 5 mg					
Nut	Cashews (Placed in same jar as walnuts)	loss of consciousness		Some nuts +febrile infection	Not determinable	Laliotou et al. 2018[20]
Nut	Pinon nut (SPT extract)	dyspnea		One drop cutaneously	Not determinable	Sindher et al. 2015[21]
Nut	Walnut	Acute anaphylactic reactions including angioedema, dyspnea, and cyanosis	1(1)	Trace amount	Not determinable	Noh et al. 2009[22]
Peanut	Peanut	Asthma	33(1)	15 mg	3.75	Moneret-Vautrin 2001[23]
Peanut	Peanut oil	Asthma	33(1)	5 mL	Not determinable	Moneret-Vautrin 2001[23]
Peanut	Peanut oil	Asthma and/or FEV↓, vomiting and/or abdominal pain	103(6)	5 mL	Not determinable	Morisset et al. 2003[24]
Peanut	Peanut oil	Asthma	62(14)	5 mL Peanut oil	Not determinable	Moneret-Vautrin et al. 1998[25]

(Continues)

TABLE 2 (Continued)

Allergen	Food product	Nature of life-threatening allergic reaction	No. of participants (no. experiencing a severe reaction)[a]	Amount of food that provoked a severe reaction	Amount of allergen protein (mg) that provoked a severe reaction	Study
Peanut	Peanut dust	Severe anaphylaxis treated with epinephrine	1(1)	Peanut dust sprinkled on meal	Not determinable	Robertson et al. 2017[26]
Sesame	Sesame seed oil	"Anaphylactic shock"	12(1)	1 mL	Not determinable	Morisset et al. 2003[24]
Sesame	Sesame seed	Throat closure, generalized urticaria, and vomiting	1(1)	5 seeds	3.15	Dua et al. 2011[27]
Soy	Soy milk	"Systemic reaction"	2(1)	0.01 mL	Not determinable	Hudes et al. 2019[28]
Sulfites	No report found for reactions at or below 5 mg					

Note: Fatal reactions were not reported at all at this level.

[a]Total number of participants in the study mentioned, while number in brackets give the number of participants experiencing the reaction described. If no number is given, only the total number of participants is listed.

formula may contain 1.08–3.6 g protein/100 ml[30] provided correct preparation. The volume of a "drop" depends on the viscosity of the liquid, however, in pharmacy and medicine, a drop is generally defined as being 0.05 mL. The amount ingested may therefore range between 1.6 mg and 5.4 mg, although given that the formula is no longer on the market, the protein content cannot reliably be verified. We therefore do not know the amount of milk protein which resulted in the described reaction. The same holds true for the reaction described by Hudes et al[28] which reported a "systemic reaction" to 0.01 ml of soy milk. However, the amount of soy protein differs widely between the different brands of soy milk, so the exact amount ingested by the patient is not determinable. Furthermore, the authors do not describe the systemic reaction in detail and any life-threatening potential cannot be determined.

Tripodi et al[14] report a case of a 11-year-old with egg allergy developing dyspnea after ingestion of a mortadella sandwich. They analyzed the mortadella and found the reactive amount being 0.45 mg hen's egg, which would mean a protein content of 0.05 mg. They did, however, not analyze the other components of the sandwich so there is no way to know if this is the real threshold dose.

Dua et al. describe one patient who experienced "throat closure" after ingestion of 5 sesame seeds. We weighed different sesame seeds on a high precision scale and found an average of 15 mg per 5 seeds, and could determine that 5 seeds contain approximately 3.15 mg sesame protein. However, the patient was not treated with epinephrine but with oral antihistamines and intravenous hydrocortisone only,[27] excluding the likelihood that treating physicians regarded it as a truly life-threatening situation.

Both, Morisset et al.[24] and Moneret-Vautrin et al.[25] described potentially life-threatening reactions after the ingestion of sesame or peanut oil. As the protein content of oil varies considerably and protein amounts have not been measured for the oils used, it is not possible to determine an amount.

Hourihane et al.,[31] Leung et al.,[32] and Lefevre et al.[15] list reactions to allergenic amounts <5 mg, but do not describe them further. Therefore, those reactions cannot be evaluated further to determine their life-threatening potential, which is acknowledged to be a problem. The same holds true for the following reports where no amounts are stated, with one of them being however a clear outlier. Robertson et al.[26] report on a criminal case where a wife spread peanut dust on her husband's meals. It can be expected that the amount was more than 5 mg protein. Poza-Guedes,[17] Paiva,[18] and Lisann[19] report potentially life-threatening reactions to accidental ingestion of trace amounts of cow's milk. As the amounts are not specified, it is not possible to determine the allergenic threshold. Laliotou[20] and Noh[22] also state "trace amounts" as triggering an anaphylactic reaction to nut. Again, the missing quantification does create a problem and it is possible that a whole nut has been ingested.

The same holds true for the report of Bansal et al.[16] where a "small amount" of lupin flour in short crust pastry triggered a reaction.

Levin et al[33] described the case of a 9-month-old child reacting with episodes of asthma, vomiting, and urticaria after ingestion of a soy formula which was contaminated with 32.4 mg milk protein

per liter. Here, it is unclear how much of the formula was administered but if it were the typical amount of one bottle containing 150–200 ml, this would be most likely more than 5mg, and furthermore, it is unclear if the reactions were life-threatening.

Yunginger et al.[34] reported 7 fatal cases, 6 of whom had eaten at least "one bite" but mostly one cookie or one piece of cake, without further specification of the amount of the relevant allergen. In one case of a fish allergic patient, French fries had been consumed, which other guests reported tasted of fish. Unfortunately, there is no way to estimate in this case, as it is unclear if the reaction was due to the sauce offered with the fries.

Azmi et al.[35] describe two cases of allergic reactions to vegan ice cream containing lupin flour, one of them potentially life-threatening. The amount of lupin flour is however not stated and is likely more than 5 mg protein since vegan ice cream usually has lupin flour as the main ingredient.

4 | DISCUSSION

4.1 | Interpretation of results

Remarkably, none of the case reports or provocation tests in a clinical setting reported a LOAEL, the lowest ingested dose at which there was an observed adverse effect, less than the evaluated threshold of 0.5 mg protein/100 g of food, to cause a life-threatening or even fatal reaction. The case reports have revealed 8 cases of fatal food allergy reactions, however, all at higher levels than 0.5mg/100 g of food. Looking at the list of the 14 different allergens which need to be declared (celery, cereals containing gluten (such as barley and oats), crustaceans (such as prawns, crabs, and lobsters), eggs, fish, lupin, milk, molluscs (such as mussels and oysters), mustard, peanuts, sesame, soybeans, sulfur dioxide, and sulfites), the following statements can be made:

No severe reactions to trace amounts of molluscs or mustard have been reported.

Sulfite is added as an allergen in the list; however, sulfite is in reality a cause for pseudoallergic reactions. Life-threatening or fatal reactions against sulfites were never reported at all. Still, it is important to also look at sulfite as severe asthmatic reactions have been described in a single report with a threshold of 50 mg.

No severe reactions have ever been reported to low amounts of any other allergen that is not listed in the 14 which have to be declared according to the EU regulations.

No fatal reactions have ever been reported with levels clearly documented below 5mg of protein for any allergen.

In a small subset of patients allergic but not life-threatening reactions can occur at levels below 5mg of protein.

The most important finding of our search is that no fatal allergic reactions to food were reported below an estimated amount of 5 mg protein.

Any interpretation of the results regarding the reporting bias should differentiate case reports of accidental reactions and provocation tests. They differ regarding the accuracy of determining the amount of allergen ingested and in classifying the reaction as "life-threatening." While case reports are very valuable, as they usually represent more accurately everyday life situations in which allergic reactions to food occur, the determination of the exact amount ingested allergen is difficult and additional cofactors like exercise, alcohol, or sleep deprivation may have influenced the manifestation or outcome of the reaction.[36] Furthermore, case reports depend partly on chance because the author has to decide if it was worth publishing. An underreporting is therefore possible but less likely for fatal cases.

For the second uncertainty, the amount of food ingested, there is a potential bias of patients tending to mention smaller amounts than truly eaten. In daily practice, a phenomenon often observed is that patients feel "guilty" and try to explain with statements such as "I hardly took a bite." Still, as stated in the methods section, the overestimation of allergen amounts was chosen generously in case reports to avoid false low assumptions leading to inappropriate reassurances. Similarly, it should be mentioned that for any ingested nut or seed that was reported in the literature, in this review, we considered the amount of the nut or seed ingested which is definitely greater or equal to the amount digested, therefore once again having potentially a slight overestimation of the total allergen protein amount, this provides a greater safety margin.

Regarding classification accuracy, the courses of actions triggering the label "life-threatening" may be more reliable in the out-of-clinic setting. Particularly when looking at the injection of epinephrine, which in our methodology categorized the case as potentially fatal, there may be great differences between case reports and provocation studies. Many studies have shown that the psychological barrier of injecting adrenaline is very high in food allergic patients and their caretakers,[37-39] resulting in a delay or an omission of intramuscular epinephrine administration.

On the other hand, handling epinephrine is routine in the clinical setting. Since those undergoing a provocation test are monitored closely, the first signs of an anaphylactic reaction will generally be noticed earlier and trigger counteractive measures, which will influence the natural course and disguise the severity of the allergic response. For example, epinephrine may be administered in cases where no life-threatening reaction would develop.

Despite the potential over-estimation in the severity of reactions in our study, categorizing all events in which epinephrine was administered as "life-threatening" increases safety, albeit at the expense of accuracy.

In accordance with the findings in this review, a cross-sectional study of food allergy prevalence in the population of Berlin by Zuberbier et al. revealed that in all open challenge tests, no adverse reaction occurred at the level of 5mg of protein.[40]

However, a study by Ballmer-Weber et al., not included in the review as it did not meet all eligibility criteria, found estimated doses eliciting reactions in 10% of the study population (ED10), as low as 1.6 to 10.1 mg of protein for hazelnut, peanut, and celery.[41] It should be noted that one limitation of this review is the defined search

criteria that may have excluded a few other publications that may contain further data regarding allergen tolerance thresholds.

This systematic review revealed that 0.5 mg/100 g as a threshold value for traces of allergens in processed food is generally a safe level for avoiding any allergic reaction to at least 6 of the 14 major allergens, even in the unlikely maximum portion size of 1 kg. Even for those allergens, a 0.5 mg/100 g threshold is highly likely to be a safe level below which fatal allergic reactions will not occur. Depending on the portion size, this level is also beneficial for the rare severely affected patients. For example, if a patient knows their personal threshold level is 2 mg they can still safely eat a portion of 100 g. However, the vast majority of all food allergic patients have a much higher threshold level for the elicitation of reactions. Very few individuals will experience symptoms below this level. Our finding of the level of 0.5 mg/100 g of food, 100 g of food being a common portion size, is in accordance with the FAO-WHO expert group recommendations on allergen thresholds, published on 20 August 2021.[120]

Based on these results, 5 mg/100 g of food is a concentration that can be used in the food industry as the safety level for most food allergy sufferers. The advantage of 5 mg/100 g of food is that it can be readily detectable for all 14 food allergens with the currently existing technology. In addition, avoiding contamination at this level should be technically feasible for the food industry as the feasibility has been discussed at three different meetings with food technologists and analytical laboratories. Rare exceptions may occur if machinery is difficult to clean. For example, pieces of nut in chocolate may be a problem, as the allergen is not evenly distributed in the food matrix.

There has also been a lot of discussion with different patient organizations which would prefer to have legally binding legislation regarding the declaration of food allergen contaminants as it remains an unmet need. However, we view the voluntary declaration as a positive direction that would benefit food allergy sufferers and their families.

Such a declaration would not only help all food allergic patients who have a known threshold above 5 mg, but it would be also helpful to the family of those patients who have anaphylaxis against allergens at levels of <1 mg, to purchase processed foods for the household, as they would be informed that the food allergic family member would not be endangered if products with possibly such low concentrations of contaminants would be used within the household. The current situation is that often the whole family of severely food allergic patients is afraid to buy any processed food at all.

In addition, physicians, dietitians, and nutritionists could better advise patients about their risk level in daily practice. This of course is mandatory for the exceedingly rare patients described in the literature who react below 5 mg protein. They should be counseled about which processed food, in general, they should avoid.

We propose as a voluntary labeling for the European Union that no traces of the 14 main food allergens in a given processed food are above 0.5 mg/100 g, together with a warning that traces below this level can occur but are likely not harmful. This message can improve the situation where manufacturers often state on the packages that traces can be contained without stating the amount of the trace, that the product has been processed in a facility which also processed, for example, peanut products. Both kinds of information are more for the sake of the producer to keep away from liability issues than for the true benefit of the consuming patient who wants to know the exact levels. The 0.5 mg/100 g level, as a clear statement on packages, would cover the vast majority of food allergic patients.

Finally, this proposal has been discussed with the food industry authorities and a statement that it is regarded as positive has been received, found in Appendix 2.

5 | LIMITATIONS

There are limitations that should be noted in the interpretation of the present work. First, due to the defined literature search query, there may be some available literature that was not identified in this review, and therefore, the data were not taken into consideration. An example would be publications on immunotherapy trials where low doses of allergen caused reactions, but they were not reported as life-threatening or fatal. Due to the large volume of hits obtained from the first round of literature screening, the publications were screened based on their title and abstract; therefore, it is possible that some data included only in the text were overseen. Also, large number of studies which were found by our search strategy did not report direct relation of the amount of allergen ingested to the observed reaction, therefore, a lot of data addressing food anaphylaxis could not be included in our analysis. It should also be taken into account that we relate to the amount of allergenic protein ingested. If the information was not reported by the investigators, it was calculated based on the usual protein content of the food product used in the provocation test or reported in the case report. Despite the careful evaluation and supervision of a professional dietitian, it cannot be ruled out that the amounts given differ from actual amount of protein ingested. It should also be mentioned that the screening of the data was done by the reviewers separately, data of uncertain relevance however was discussed by all three reviewers. Lastly, the summary of case reports may give the impression that in most cases the dose amount is unknown, suggesting that the information is incomplete and insufficient. As case reports are a valuable data source of real-life situations, it is an unmet need to standardize the investigation and tracking of fatality in food allergy.

6 | CONCLUSIONS

No fatal reactions have been reported below 5 mg of protein exposure in food allergic patients. The individual eliciting threshold differs considerably between patients, but the vast majority of patients do not react at levels below 5 mg of protein. For these patients, it would be helpful to know that contamination with allergens in processed food does not exceed this level. Looking at a further safety margin, it is therefore proposed that 5mg/kg of contaminating

allergen in processed food is not exceeded acknowledging that the usual portion size is far lower than 1 kg.

The labeling could read as follows: "this product contains the named allergens in the list of ingredients, it may contain traces of other contaminants (to be named, e.g. nut) at concentrations less than 0.5 mg per 100g of this product" for a voluntary declaration on processed food packages.

We further see this only as a first step as legally binding thresholds would be preferred. The authors however feel that realistically it would take a long time before this will be implemented on a global scale, and in the meantime, the more precise the labeling is the better.

Furthermore, we conclude that also this review is only a first step in research concentrating on a threshold to avoid fatal reactions, more research is needed to identify thresholds for milder symptoms of food allergy.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

ORCID

Torsten Zuberbier https://orcid.org/0000-0002-1466-8875
Montserrat Alvaro https://orcid.org/ 0000-0002-5528-8043
Stefania Arasi https://orcid.org/0000-0002-8135-0568
Hasan Arshad https://orcid.org/0000-0001-5988-235X
Joan Bartra https://orcid.org/0000-0001-7767-4730
Lisa Beck https://orcid.org/0000-0002-8452-667X
Philippe Bégin https://orcid.org/0000-0002-9089-4604
Carsten Bindslev-Jensen https://orcid.org/0000-0002-8940-038X
Jean Bousquet https://orcid.org/0000-0002-4061-4766
Knut Brockow https://orcid.org/0000-0002-2775-3681
Andrew Bush https://orcid.org/0000-0001-6756-9822
Antonella Cianferoni https://orcid.org/0000-0002-2966-2564
Michael J. Cork https://orcid.org/0000-0003-4428-2428
Adnan Custovic https://orcid.org/0000-0001-5218-7071
Stefano Del Giacco https://orcid.org/0000-0002-4517-1749
Antoine Deschildre https://orcid.org/0000-0003-2006-7221
Motohiro Ebisawa https://orcid.org/0000-0003-4117-558X
Montserrat Fernández-Rivas https://orcid.org/0000-0003-1748-2328
Marta Ferrer https://orcid.org/0000-0001-8495-1302
Alessandro Fiocchi https://orcid.org/0000-0002-2549-0523
Roy Gerth van Wijk https://orcid.org/0000-0002-9608-8742
Maia Gotua https://orcid.org/0000-0003-2497-4128
Enrico Heffler https://orcid.org/0000-0002-0492-5663
Michihiro Hide https://orcid.org/0000-0002-1569-6034
Karin Hoffmann-Sommergruber https://orcid.org/0000-0002-8830-058X
Cristoforo Incorvaia https://orcid.org/0000-0002-3965-7988
Christer Janson https://orcid.org/0000-0001-5093-6980
Norito Katoh https://orcid.org/0000-0002-3498-2482
Benjamin Kendziora https://orcid.org/0000-0002-5234-5380
Tamar Kinaciyan https://orcid.org/0000-0002-8238-2561
Oksana Kurbacheva https://orcid.org/0000-0003-3250-0694
Susanne Lau https://orcid.org/0000-0002-5189-4265
Carlo Lombardi https://orcid.org/0000-0002-8040-0324
Michael Makris https://orcid.org/0000-0003-2713-2380
Marcus Maurer https://orcid.org/0000-0002-4121-481X
Rosan Meyer https://orcid.org/0000-0002-5710-5570
Dragan Mijakoski https://orcid.org/0000-0002-3291-0661
Jordan Minov https://orcid.org/0000-0002-9870-4756
Joaquim Mullol https://orcid.org/0000-0003-3463-5007
Caroline Nilsson https://orcid.org/0000-0003-2040-8428
Anna Nowak–Wegrzyn https://orcid.org/0000-0002-0960-9854
Bright I. Nwaru https://orcid.org/0000-0002-2876-6089
Giovanni Battista Pajno http://orcid.org/0000-0002-6897-4587
Sushil Paudel https://orcid.org/0000-0001-8665-5355
Nikolaos G. Papadopoulos https://orcid.org/0000-0002-4448-3468
Harald Renz https://orcid.org/0000-0003-0602-7215
Giampaolo Ricci https://orcid.org/0000-0002-3660-8750
Hugh Sampson https://orcid.org/0000-0003-1613-8875
Brigita Sitkauskiene https://orcid.org/0000-0001-5086-8893
Peter Kenneth Smith https://orcid.org/0000-0002-2629-8963
Katarina Stevanovic https://orcid.org/0000-0003-3930-9761
Sasho Stoleski https://orcid.org/0000-0003-1278-903X
Hania Szajewska https://orcid.org/0000-0002-4596-2874
Akio Tanaka https://orcid.org/0000-0002-5354-7064
Fatih Alexander Topal https://orcid.org/0000-0003-1340-105X
Ronald Van Ree https://orcid.org/0000-0003-0767-0894
Carina Venter https://orcid.org/0000-0002-7473-5355
Stefan Wöhrl https://orcid.org/0000-0002-6324-0007
Gary W.K. Wong https://orcid.org/0000-0001-5939-812X
Zuotao Zhao https://orcid.org/0000-0002-9595-6050
Margitta Worm https://orcid.org/0000-0002-3449-1245

REFERENCES

References 42–119 have been cited in Supporting Information.

1. Pepper AN, Assa'ad A, Blaiss M, et al. Consensus report from the Food Allergy Research & Education (FARE) 2019 oral immunotherapy for food allergy summit. *J Allergy Clin Immunol*. 2020;146(2):244-249.
2. Warren CM, Otto AK, Walkner MM, Gupta RS. Quality of life among food allergic patients and their caregivers. *Curr Allergy Asthma Rep*. 2016;16(5):38.
3. Marchisotto MJ, , Harada L, Kamdar O, et al. Food allergen labeling and purchasing habits in the United States and Canada. *J Allergy Clin Immunol Pract*. 2017;5(2):345-351.e2.

4. Shoji M, Adachi R, Akiyama H. Japanese food allergen labeling regulation: an update. *J AOAC Int*. 2018;101(1):8-13.
5. Beer M. Informationsschreiben Nr. 161: Allergenkennzeichnung von unbeabsichtigten Vermischungen (Art. 8 Abs. 3-5 der Verordnung über die Kennzeichnung und Anpreisung von Lebensmitteln, LKV) Stand: 18.04.2011, ersetzt die Version vom 17.12.2010, B.f.G. BAG, Editor. 2011, Bern.
6. Richter K, Kramarz S, Niemann B, et al. Schwellenwerte zur Allergenkennzeichnung von Lebensmitteln, in Allergien: Bessere Information, höhere Lebensqualität, B.f. Risikobewertung, Editor. 2009, Bundesinstitut für Risikobewertung: Berlin.
7. Allergen Bureau VITAL® best practice labelling guide For Australia and New Zealand. 2016.
8. Röder M, Weber W. VITAL – ("Voluntary Incidental Trace Allergen Labelling"). 2020 [cited 2020 8th July 2020]; Available from: https://www.produktqualitaet.com/de/inspektionen/allergenmanagement/risikobewertung-vital.html
9. Bf R. "VITAL 3.0": Neue und aktualisierte Vorschläge für Referenzdosen von Lebensmittelallergenen - Stellungnahme Nr. 015/2020 des BfR vom 9. März 2020. In: Risikobewertung Bf, editor., 2020.
10. Remington BC, Westerhout J, Meima MY, et al. Updated population minimal eliciting dose distributions for use in risk assessment of 14 priority food allergens. *Food Chem Toxicol*. 2020;139:111259.
11. Allen KJ, Remington BC, Baumert JL, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J Allergy Clin Immunol*. 2014;133(1):156-164.
12. Allergen Bureau Summary of the 2019 VITAL Scientific Expert Panel Recommendations, A. Bureau, Editor. 2019.
13. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*. 2009;6(7):e1000097.
14. Tripodi S, et al. An anphylactic shock in a 11-year-old girl by hidden hens' egg in mortadella (a large Italian sausage). *Allergy*. 2009;90:566.
15. Lefevre S, Kanny G. Oral immunotherapy and omalizumab for food allergy. *Allergy*. 2016;71(suppl 102):269.
16. Bansal AS, Sanghvi MM, Bansal RA, Hayman GR. Variably severe systemic allergic reactions after consuming foods with unlabelled lupin flour: a case series. *J Med Case Rep*. 2014;55 (no pagination)(55).1–4.
17. Poza-Guedes P, González-Pérez R, Sánchez-Machín I, Matheu V. Long-term follow up in cow's milk anaphylaxis after successful rush oral immunotherapy. *J Allergy Clin Immunol*. 2014;1:AB106.
18. Paiva M, et al. Successful oral rush desensitisation in two children with severe cow's milk allergy. *Allergy*. 2009;90:487.
19. Lisann L, Song Y, Wang J, Ehrlich P, Maitland A, Li X-M. Successful prevention of extremely frequent and severe food anaphylaxis in three children by combined traditional Chinese medicine therapy. *Allergy Asthma Clin Immunol*. 2014;66 (no pagination)(66).1–6.
20. Laliotou NN, et al. Anaphylaxis with the manifestation of convulsions. *Allergy*. 2018;73(suppl 105):357.
21. Sindher SB, DaVeiga SP. Acute anaphylaxis following fresh food skin prick testing with pine nuts. *Ann Allergy Asthma Immunol*. 2015;1:A6.
22. Noh G, Lee SS. A pilot study of interferon-gamma-induced specific oral tolerance induction (ISOTI) for immunoglobulin E-mediated anaphylactic food allergy. *J Interferon Cytokine Res*. 2009;29(10):667-675.
23. Moneret-Vautrin DA, et al. Food anaphylaxis in schools: evaluation of the management plan and the efficiency of the emergency kit. *Allergy*. 2001;56(11):1071-1076.
24. Morisset M, Moneret-Vautrin DA, Kanny G, 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(8):1046-1051.
25. Moneret-Vautrin DA, Rance F, Kanny G, et al. Food allergy to peanuts in France–evaluation of 142 observations. *Clin Exp Allergy*. 1998;28(9):1113-1119.
26. Robertson K, Kim H. Intentional poisoning with peanut as a cause of recurrent anaphylaxis. Allergy, Asthma and Clinical Immunology. Conference: Canadian Society of Allergy and Clinical Immunology Annual Scientific Meeting, 2017. **14**(Supplement 1).
27. Dua S, Wagner A, Ewan PW. The role of tryptase and food challenge in diagnosing IgE negative sesame seed allergy. *Clin Exp Allergy*. 2011;41:1822-1865.
28. Hudes G, Friedman N, Rosenstreich D. Soy milk anaphylaxis in patients with negative soy specific ige and skin test: diagnostic challenge. *Abstracts: Medically Challenging Cases Abstracts/Ann Allergy Asthma Immunol*. 2019;123.S64–S142.
29. Ebrahimi M, Gharagozlou M, Mohebbi A, et al. The efficacy of oral immunotherapy in patients with cow's milk allergy. *Iran J Allergy Asthma Immunol*. 2017;16(3):183-192.
30. SCo, F. Report of the scientific committee on food on the revision of essential requirements of infant formulae and follow-on formulae. 2003: In: DIRECTORATE-GENERAL ECHaCP, editor.
31. Hourihane J, Knulst A. Thresholds of allergenic proteins in foods. *Toxicol Appl Pharmacol*. 2005;207:S152-S156.
32. Leung DY, et al. New approaches for the treatment of anaphylaxis. *Novartis Found Symp*. 2004;257:248-260; discussion 260-4, 276-85.
33. Levin ME, Motala C, Lopata AL. Anaphylaxis in a milk-allergic child after ingestion of soy formula cross-contaminated with cow's milk protein. *Pediatrics*. 2005;116(5):1223-1225.
34. Yunginger JW, Sweeney KG, Sturner WQ, et al. Fatal food-induced anaphylaxis. *J Am Med Assoc*. 1988;260(10):1450-1452.
35. Azmi S, Simpson A, Chew F, Marinho S. Two cases of allergy to Lupin in vegan ice-cream. *Allergy*. 2019;74:489.
36. Worm M, Francuzik W, Renaudin J-M, et al. Factors increasing the risk for a severe reaction in anaphylaxis: an analysis of data from the European Anaphylaxis Registry. *Allergy*. 2018;73(6):1322-1330.
37. Marrs T, Lack G. Why do few food-allergic adolescents treat anaphylaxis with adrenaline?–Reviewing a pressing issue. *Pediatr Allergy Immunol*. 2013;24(3):222-229.
38. Song TT, Worm M, Lieberman P. Anaphylaxis treatment: current barriers to adrenaline auto-injector use. *Allergy*. 2014;69(8):983-991.
39. Kim JS, Sinacore JM, Pongracic JA. Parental use of EpiPen for children with food allergies. *J Allergy Clin Immunol*. 2005;116(1):164-168.
40. Zuberbier T, Edenharter G, Worm M, et al. Prevalence of adverse reactions to food in Germany - a population study. *Allergy*. 2004;59(3):338-345.
41. Ballmer-Weber BK, Fernandez-Rivas M, Beyer K, et al. How much is too much? Threshold dose distributions for 5 food allergens. *J Allergy Clin Immunol*. 2015;135(4):964-971.
42. Kothra A, Galani M, Xepapadaki P, et al. Oral food challenges to nuts in children with LTP sensitization. *J Allergy Clin Immunol*. 2019;74(suppl 106):506-507.
43. Alviani C, Burrell S, Macleod A, et al. Anaphylaxis refractory to intramuscular adrenaline during in-hospital food challenges: a case series and proposed management. *Clin Exp Allergy*. 2020;50(12):1400-1405.
44. Grabenhenrich LB, Dölle S, Moneret-Vautrin A, et al. Anaphylaxis in children and adolescents: the European Anaphylaxis Registry. *J Allergy Clin Immunol*. 2016;137(4):1128-1137.e1.
45. Gruzelle V, Juchet A, Martin-Blondel A, Michelet M, Chabbert-Broue A, Didier A. Benefits of baked milk oral immunotherapy in French children with cow's milk allergy. *Pediatr Allergy Immunol*. 2020;31(4):364-370.

46. Nakamura T, Okada Y, Maeda M, Kamiya T, Imai T. Oral food challenges using multiple-dose steps for cow's milk allergy: safety and efficiency. *Allergy*. 2020;75(suppl 109):269.
47. Rha J, Lanser P, Hauk P. A case of severe anaphylaxis to baked milk in a child on dupilumab. *Ann Allergy Asthma Immunol*. 2020;125(suppl 5):S102.
48. Ruano FJ, Prieto-Moreno Pfeifer A, Torres I, et al. Experience with Omalizumab in patients with anaphylactic reactions to milk allergy. *Allergy*. 2019;74:(S106):356. –. http://doi.org/10.1111/all.13960
49. Sato S, et al. Underlying mechanisms of oral immunotherapy against hen's egg and cow's milk anaphylaxis. *Allergy*. 2011;94):397.
50. Takahashi M, Taniuchi S, Soejima K, Hatano Y, Yamanouchi S, Kaneko K. Successful desensitization in a boy with severe cow's milk allergy by a combination therapy using omalizumab and rush oral immunotherapy. *Allergy Asthma Clin Immunol*. 2015;11(1):18.
51. Tejero Alcalde M, Rojas Perez-Ezquerra P, Fuentes AV. Cow's milk desensitization in a 23-year-old man. *Allergy*. 2019;74(S106):802.
52. Yanagida N, Utsunomiya T, Sato S, et al. Treatment of hen's egg- and cow's milk-induced anaphylaxis by rash oral immunotherapy. *J Allergy Clin Immunol*. 2010;125:AB26.
53. Turner PJ, Mehr S, Joshi P, et al. Safety of food challenges to extensively heated egg in egg-allergic children: a prospective cohort study. *Pediatr Allergy Immunol*. 2013;24:450-455.
54. Pacharn P, et al. Wheat-dependent, exercise-induced anaphylaxis in Thai children: a report of 5 cases. *Asian Pac J Allergy Immunol*. 2009;27:115-120.
55. Asaumi T, Yanagida N, Sato S, Shukuya A, Nishino M, Ebisawa M. Provocation tests for the diagnosis of food-dependent exercise-induced anaphylaxis. *Pediatr Allergy Immunol*. 2016;27(1):44-49.
56. Matsukura S, Aihara M, Sugawara M, et al. Two cases of wheat-dependent anaphylaxis induced by aspirin administration but not by exercise. *Clin Exp Dermatol*. 2010;35(3):233-237.
57. Matsuo H, Morimoto K, Akaki T, et al. Exercise and aspirin increase levels of circulating gliadin peptides in patients with wheat-dependent exercise-induced anaphylaxis. *Clin Exp Allergy*. 2005;35(4):461-466.
58. Thongngarm T, Wongsa C, Pacharn P, Piboonpocanun S, Sompornrattanaphan M. Clinical characteristics and proposed wheat-cofactor challenge protocol with a high diagnostic yield in adult-onset IgE-mediated wheat allergy. *J Asthma Allergy*. 2020;13:355-368.
59. Ueno R, Takaoka Y, Shimojo N, et al. A case of pediatric anaphylaxis caused by gummy tablets containing fish collagen. *Asia Pac Allergy*. 2020;10(4):e35.
60. Dereci S, Koca T, Akcam M. The incidence and clinical characteristics of IgE-mediated hazelnut allergy in children living in the eastern black sea region of Turkey. *Pediatr Allergy Immunol Pulmonol*. 2016;29(1):24-28.
61. Fink W, Capucilli P, Lewis MO, Rooney CB, Brown-Whitehorn TF. Significantly increased threshold dose after long-term peanut epicutaneous immunotherapy and daily oral peanut intake. *Ann Allergy Asthma Immunol*. 2019;123(suppl 5):S86-S87.
62. Oppenheimer JJ, et al. Treatment of penaut allergy with rush immunotherapy. *J Allergy Clin Immunol*. 1992;90(2):256-262.
63. Mendez Reyes J, Pistiner M., P.M. Peanut induced anaphylaxis in an infant oral food challenge requiring two doses of epinephrine. *Ann Allergy Asthma Immunol*. 2019;123(suppl 5):S126.
64. Van Erp FC, et al. Can we predict severe reactions during peanut challenges in children? *Pediatr Allergy Immunol*. 2013;24(6):596-602.
65. Nagakura K, et al. Two year follow-up after rush oral immunotherapy for peanut-induced anaphylaxis. *Allergy*. 2015;101:181.
66. Nagakura K-I, Sato S, Yanagida N, et al. Oral immunotherapy in Japanese children with anaphylactic peanut allergy. *Int Arch Allergy Immunol*. 2018;175(3):181-188.
67. Lindvik H, Lødrup Carlsen KC, Mowinckel P, Navaratnam J, Borres MP, Carlsen K-H. Conjunctival provocation test in diagnosis of peanut allergy in children. *Clin Exp Allergy*. 2017;47(6):785-794.
68. Salari F, Bemanian MH, Fallahpour M, 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(1):27-34.
69. Yoshihiro T, Matsui T, Suguira S, Ito K. Oral immunotherapy for 7 patients with sesame allergy. *Eur J Allergy Clin Immunol*. 2019;74:799.
70. Inomata N, Osuna H, Kawano K, et al. Late-onset Anaphylaxis after Ingestion of Bacillus Subtilis-fermented Soybeans (Natto): clinical review of 7 patients. *Allergol Int*. 2007;56:257-261.
71. Yang WH, Purchase ECR, Rivington RN. Positive skin tests and Prausnitz-Küstner reactions in metabisulfite-sensitive subjects. *J Allergy Clin Immunol*. 1986;78(3):443-449.
72. Koike Y, Yanagida N, Sato S, et al. Predictors of persistent wheat allergy in children: a retrospective cohort study. *Int Arch Allergy Immunol*. 2018;176:1-6.
73. Phisitbuntoon T, Jirapongsananuruk O, Pacharn P, et al. A potential role of gliadin extract skin prick test in IgE-mediated wheat allergy. *Asian Pac J Allergy Immunol*. 2020. https://doi.org/10.12932/AP-291119-0703
74. Utsunomiya T, Imai T, Ogura K, et al. Rush oral immunotherapy for wheat-induced anaphylaxis in Japan. *J Allergy Clin Immunol*. 2012;1):AB26.
75. Rekabi M, Arshi S, Darougar S, et al. Oral wheat immunotherapy in a patient with anaphylaxis despite negative sensitization tests. *Shiraz E-Med J*. 2019;20(2):e83309.
76. Vichyanond P, Visitsuntorn N, Tuchinda M. Wheat-induced anaphylaxis. *Asian Pac J Allergy Immunol*. 1990;8(1):49-52.
77. Herzinger T, Kick G, Ludolph-Hauser D, Przybilla B. Anaphylaxis to wheat beer. *Ann Allergy Asthma Immunol*. 2004;92(6):673-675.
78. Barber C, Kalicinsky C. A novel combination of an IgE mediated adult onset food allergy and a suspected mast cell activation syndrome presenting as anaphylaxis. *Allergy Asthma Clin Immunol*. 2016;12(14) (no pagination)(46).2–4.
79. Lee TK, Huntwork MP, Carlson JC. Too old for egg allergya case of anaphylaxis in the elderly. *J Gen Intern Med*. 2018;33(2 suppl 1):648.
80. Niggemann B, Yurek S, Beyer K. Severe anaphylaxis requiring intensive care during oral food challenge-It is not always peanuts. *Pediatr Allergy Immunol*. 2017;28(2):201-203.
81. Mikos N, et al. Adult onset anaphylaxis to egg yolk. *Allergy*. 2012;96:381.
82. Hirata J-I, Ohya M, Kumon K. Diagnosis and long-term management of hydrolyzed wheat protein wheat-dependent exercise-induced anaphylaxis. *Acute Med Surg*. 2015;2:260-262.
83. Muñoz FM, López Cazaña JM, Villas F, Contreras JF, Díaz JM, Ojeda JA. Exercise-induced anaphylactic reaction to hazelnut. *Allergy*. 1994;49:314-316.
84. Kham Murng SH, Egner W, Shrimpton A, Sargur RB. Using Omega-5 Gliadin (rTri a 19) in the diagnosis ofanaphylaxis. *J Allergy Clin Immunol*. 2013;131(2):AB214.
85. Nardi M, Lin R-W. Food associated exercise induced anaphylaxis associated with late phase skin test reactivity to shrimp. *J Allergy Clin Immunol*. 2014;133(2):27.
86. Suksawat Y. Food-dependent exercise-induced anaphylaxis in 17-year-old adolescent male. *Allergy*. 2018;73(suppl 105):789.
87. Dongo LC, et al. Celery-dependent exercise induced anaphylaxis confirmed only by BAT. *Allergy*. 2014;99:276.
88. Hameed O, Skibinska M. Food-dependent exercise-induced anaphylaxis: A series of three cases. *Br J Dermatol*. 2012;1:150-151.
89. Mobayed HM, Ali Al-Nesf M. Two cases of food-dependent exercise-induced anaphylaxis with different culprit foods. *Ann Thorac Med*. 2014;9(1):42-44.

90. Witten M, et al. Fish dependent exercise-induced anaphylaxis after ingestion of a high dose of salmon. *Allergy*. 2014;99:278.
91. Lin HY, et al. Fish induced anaphylactic reaction: report of one case. *Zhonghua Min Guo Xiao Er Ke Yi Xue Hui Za Zhi*. 1998;39(3):200-202.
92. Makatsori M, Cappella A, McKenzie R, Skypala I. Anaphylaxis-don't forget lupin! *Clin Transl Allergy*. 2013;3(suppl 3):P158.
93. Soller L, La Vieille S, Chan ES. First reported case in Canada of anaphylaxis to lupine in a child with peanut allergy. *Allergy Asthma Clin Immunol*. 2018;14(64) (no pagination)(64).1–3.
94. Bito T, Kanda E, Tanaka M, Fukunaga A, Horikawa T, Nishigori C. Cows milk-dependent exercise-induced anaphylaxis under the condition of a premenstrual or ovulatory phase following skin sensitization. *Allergol Int*. 2008;57(4):437-439.
95. Dahdah L, Ceccarelli S, Amendola S, et al. IgE Immunoadsorption knocks down the risk of food-related anaphylaxis. *Pediatrics*. 2015;136(6):e1617-e1620.
96. David TJ. Anaphylactic shock during elimination diets for severe atopic eczema. *Arch Dis Child*. 1984;59(10):983-986.
97. Ameratunga R, Woon ST. Anaphylaxis to hyperallergenic functional foods. *Allergy Asthma Clin Immunol*. 2010;6(33) (no pagination)(33).1–6.
98. Dias JG, Costa AC, Pedro E, Barbosa MP. Specific oral tolerance induction (SOTI) to cow's milk in an adult patient with anaphylaxis symptoms. *Allergy*. 2011;94):239.
99. Tripodi S, et al. Severe anaphylaxis to sheep's milk cheese in a child desensitized to cow's milk through specific oral tolerance induction. *Eur Ann Allergy Clin Immunol*. 2013;45(2):56-60.
100. Lazar I, Cavari Y, Levitas A, Mandolla AB, Broides A. Gastric drainage in the treatment of near-fatal food-induced anaphylaxis. *Pediatr Emerg Care*. 2017;09:9.
101. Dias JG, Costa AC, Pedro E, Barbosa MP. Specific oral tolerance induction (SOTI) to cow's milk in an adult patient with anaphylaxis symptoms. In Clinical and Translational Allergy. Conference: Food Allergy and Anaphylaxis Meeting 2011.
102. Marguet C, Couderc L, Blanc T,. et al. Anaphylaxis in children and adolescents: apropos of 44 patients aged 2 months to 15 years. *Arch Pediatr*. 1999;1(suppl 6):72S-78S.
103. Garcia Sifuentes L, et al. Life-threatening anaphylaxis in an adult patient monosensitised to almond: a case report. *Allergy*. 2009;90:365.
104. Lai J, Campbell D. Always be prepared. *Intern Med J*. 2016;46(suppl 4):30.
105. Koepke JW, et al. Anaphylaxis to pinon nuts. *Ann Allergy*. 1990;65(6):473-476.
106. Meysman M, Schelfaut D, Vincken W. A not so healthy muesli: a case report. *Acta Clin Belg*. 2009;64(4):366-368.
107. Barbarroja-Escudero J, et al. Severe allergic reaction to pine nut. *Allergy*. 2012;96:382.
108. Lall P, Lodi U. The deadly dessert: transfer of food allergy following lung transplantation from donor to recipient. *Ann Allergy Asthma Immunol*. 2013;1:A28.
109. Dehlink E, Bannert C, Eiwegger T, Diesner S, Gruber S, Szépfalusi Z. Omalizumab as successful treatment option in severe peanut allergy. *Clin Transl Allergy*. 2013;3(S3):20.
110. Foucard T, Malmheden Yman I. A study on severe food reactions in Sweden–is soy protein an underestimated cause of food anaphylaxis? *Allergy*. 1999;54(3):261-265.
111. Khalid I, Zoratti E, Stagner L, Betensley AD, Nemeh H, Allenspach L. Transfer of peanut allergy from the donor to a lung transplant recipient. *J Heart Lung Transplant*. 2008;27(10):1162-1164.
112. Jonsson-Razdan P, et al. A case of peanut induced anaphylaxis and the development ofa thoracolumbar syrinx. *Ann Allergy Asthma Immunol*. 2011;1:A24.
113. Lindsley S, et al. Refractory anaphylaxis at food challenge treated with peripheral adrenaline infusion. *Clin Exp Allergy*. 2017;47(12):1704.
114. Chatain C, Pin I, Pralong P, Jacquier JP, Leccia MT. A severe anaphylactic reaction to peanut after a negative challenge test [French]. *Rev Fr Allergol*. 2016;56(2):94-97.
115. Kagi MK, Wuthrich B. Falafel burger anaphylaxis due to sesame seed allergy. *Ann Allergy*. 1993;71(2):127-129.
116. D'Amelio CM, et al. Anaphylaxis due to sesame seed food allergy with negative skin prick tests: the hydrophilic fraction also matters. *Allergy*. 2015;101:490.
117. Carrusca C, et al. Soy anaphylaxis in an infant: a case report. *Allergy*. 2014;99:386.
118. Asero R, et al. Unusual allergy to soy appeared in adult age. *Eur Ann Allergy Clin Immunol*. 2016;48(3):94-96.
119. Ojeda PM, Ojeda I, Rubio G. Anaphylaxis due to sulfite intolerance: a protective effect from cyanocobalamin. *Clin Transl Allergy*. 2013;3(suppl 3):P15.
120. FAO-WHO. Summary report of the 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. 2021.

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