ILSI North America

1156 Fifteenth Street, NW
Suite 200
Washington, DC 20005

1.202.659.0074 voice
1.202.659.3859 fax
www.ilsina.org

FR Notice: Request for Comments and Information on Initiating a Risk Assessment for Establishing Food Allergen Thresholds; Establishment of Docket Docket No. FDA-2012-N-0711

The North American branch of the International Life Sciences Institute (ILSI) commends the United States Department of Health & Human Services (DHHS), Food and Drug Administration (FDA) for establishing a docket to obtain comments relevant to conducting a risk assessment to establish regulatory thresholds for major food allergens as defined in the Food Allergen Labelling and Consumer Protection Act of 2004. ILSI North America appreciates the opportunity to provide comments on behalf of ILSI to the FDA Federal Register Notice Docket No. FDA-2012-N-0711.

ILSI is a nonprofit, worldwide foundation established in 1978 to advance the understanding of scientific issues related to nutrition, food safety, toxicology, risk assessment, and the environment by bringing together scientists from academia, government, industry, and the public sector to solve problems with broad implications for the well-being of the general public. ILSI works through regional branches and other entities, the largest of which include ILSI North America, ILSI Europe, and ILSI Japan. ILSI North America is a public, non-profit foundation that provides a forum to advance understanding of scientific issues related to the nutritional quality and safety of the food supply by sponsoring research programs, educational seminars and workshops, and publications. ILSI North America receives support primarily from its industry membership. ILSI North America's scientific programs in support of public health are guided in significant part by the expert advice and intellectual contributions of more than 50 academic advisors and government liaisons. We value these collaborative relationships very highly, because they bring a wealth of knowledge and experience, and a diversity of viewpoints, that ensure the precision, balance, and integrity of our work.

The ILSI North America Technical Committee on Food and Chemical Safety supports the Food Allergy Resource and Research Program's (FARRP) approach to focus on quantitative probabilistic risk assessment for establishing thresholds. The Committee commissioned a peanut data set that FARRP

researched and published in 2010. This manuscript is included as part of our submission and is discussed in further detail under question #3.

In 2012, ILSI Europe organized a Workshop on "Food Allergy: From Thresholds to Action Levels" in collaboration with The Food Allergy Research & Resource Program (FARRP), Health Canada's Food Directorate, ILSI North America Technical Committee on Food and Chemical Safety, ILSI Japan and the University of Nebraska. The workshop was held in September 2012 in Reading, UK. The goal and purpose of the workshop was to share the work of a global Expert Group and to foster a consensus with respect to the feasibility of defining reference values for use in the management of allergenic foods, thereby reducing risk and improving safety for food allergic consumers. It was recognized that over the last few years, considerably more low-dose challenge data have become available and tools to analyze these data and apply them to quantitative risk assessment have also continued to develop. Population dose distributions for many major regulated allergens have thus been developed and risk models elaborated to estimate the impact of defined contamination patterns within the specific population of allergic consumers.

The Expert Group drafted an Expert Report in advance of the workshop. The composition of the Expert Group included individuals with expertise in the field and representative of the different stakeholder groups. The list of Expert Group members is provided as an attachment to the comments. This report served as the foundation for the discussions at the workshop involving all stakeholders, including patient groups, government scientists and food industry scientists. The Expert Report adopted the reference dose proposals of the VITAL Scientific Expert Panel set up by the Australian Allergen Bureau and examined how they could be applied operationally. This included consideration of data quality, uncertainty factors and consumer behaviour, particularly in relation to precautionary labelling. It also identified data and knowledge gaps.

The Workshop Draft Report on "Food Allergy: From Thresholds to Action Levels" describes and discusses how reference doses derived from dose distribution modelling of controlled food challenge results can be used to develop an evidence-based framework for assessing the risk from cross-contact in foods for normal consumption. It is not intended to provide the basis for claiming that a product is "free-

from" a specific allergen. Furthermore the risk assessment framework excludes issues of labelling of allergenic ingredients present in very small amounts, which is based on their presence alone, in accordance with relevant legislation.

The output of the Workshop on "Food Allergy: From Thresholds to Action Levels" consists of the preparation of three manuscripts, covering three major topics; 1) Establishment of reference doses for food allergens in line with standard toxicological principles (i.e., NOAEL, LOAEL, referencing dose, etc.); 2) Model for translating reference doses to action levels and; 3) Intake data requirements for use in food allergen risk assessment. The three manuscripts are in the process of submission for publication. ILSI North America plans to submit the three manuscripts to the FDA as part of the agency's information gathering once the manuscripts have been accepted for publication.

In the interim, we believe that the FDA will find informative the ILSI Europe workshop presentations, which are available online at: http://www.ilsi.org/Europe/Pages/ViewEventDetails.aspx?WebId=84D7FA4A-0FD5-40CD-A49A-2DA6FCDFD654&ListId=178B3510-408A-4E59-ADE5-DF09F4E38F03&ItemID=103

III. Establishment of a Docket and Request for Information

ILSI North America identified three published manuscripts and highlights provided in quotes from the Workshop Draft Report to respond specifically to Questions #1-5 and #7 in the FR Notice.

1) **How should we define "an allergic response that poses a risk to human health?"**

Two sections from the Workshop Draft Report are highlighted below that are relevant to Question #1.

"A food is identified as allergenic, because individuals are reported to react to it in a manner consistent with reactions mediated by Immunoglobulin E (IgE). An allergic response is completed by demonstration of IgE binding to individual proteins in the food and confirmatory tests including clinical controlled oral challenges in affected individuals. Currently only reaction in sensitized individuals can be considered

adequate confirmation that a food is allergenic. An allergic response, or hazard identification, therefore relies completely on human data from previously exposed and sensitized individuals."

"Preventing all types of reaction in all allergic individuals would be trying to achieve zero risk, which is not a realistic possibility. The severity of adverse events varies significantly between persons with a food allergy and depends on the nature and properties of the allergen, the consumed amount of the allergen and the physiological and genetic background of the patient. A prerequisite for public health authorities is therefore to share a broadly similar outlook on the frequency of food allergic reactions that could be accepted, differentiating between reactions of different degrees of severity and aligned with the actual needs and behaviour of allergic consumers. The protection of allergic consumers is a shared responsibility and regulators across the EU and beyond should make that decision in consultation with all interested parties, including allergic consumers, patient organizations, food businesses, scientists and health care professionals (i.e. medical doctors, health centre physicians, and dieticians) and public authorities. Agreement with those stakeholders on what can be achieved and the resulting risk management objectives would form a sound basis for progress, building on existing evidence about risk perception and behaviours (Health Council of the Netherlands 2007; Madsen et al 2012). Once the political level has taken a decision on the tolerable frequency of different types of adverse allergic effects, as discussed above, allergen reference doses can be determined which meet the appropriate level of protection and can be used by businesses and regulators to assess the levels of allergen cross contamination that have been detected in a particular product. If a business is able to ensure that this reference dose would not be exceeded by eating a serving of the food in question the precautionary labelling should be omitted on that particular product (Health Council of the Netherlands 2007). Any given benchmark, such as a reference dose, actually protects to a greater degree than the nominal level of protection. If a business is controlling allergen cross contamination to a certain level, almost all products will in fact contain lower levels of the allergenic food, if it is there at all, although there is still a risk that the allergenic food could be present at that action level. Moreover, most patient challenges are conducted using model foods designed to maximize 'bioavailability, which in real food products may be less due to the effects of food processing and cooking and interactions with the matrix components, such as fats."

2) **Which major food allergens are of greatest public health concern and what is the size of the at-risk population?**

In the United States, eight major allergens have been identified: milk, egg, fish, crustacean shellfish, tree nuts, wheat, peanuts, and soybeans.

ILSI North America submits two manuscripts from the work of the ILSI Europe Food Allergy Task Force that addresses the question of the size of the at-risk population.

a) "Application of scientific criteria to food allergens of public health importance" Y.J. Chung, S. Ronsmans, R.W.R. Crevel, G.F. Houben, R.J. Rona, R. Ward, A. Baka *Regulatory Toxicology and Pharmacology* 64 (2012) 315-323.
b) "Evaluation of scientific criteria for identifying allergenic foods of public health importance" J.H.M. van Bilsen, S. Ronsmans, R.W.R. Crevel, R.J. Rona, H. Przyrembel, A.H. Penninks, L. Contor, G. F. Houben. *Regulatory Toxicology and Pharmacology* 60 (2011) 281-289.

Those papers also describe a systematic, evidence-based approach to identifying potential allergens that should be regulated in the future.

3) **How should clinical dose distribution data be used when establishing regulatory thresholds for the major food allergens?**

The ILSI North America Technical Committee on Food and Chemical Safety supports the Food Allergy Resource and Research Program's (FARRP) approach to focus on probabilistic risk assessment for establishing thresholds. The Committee commissioned a peanut data set that FARRP researched and published in 2010.

The manuscript, "Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals" S.L. Taylor, D.A. Moneret Vautrin, R.W.R. Crevel, D. Sheffield, M. Morisset, P. Dumont, B.C. Remington, J.L. Baumert Food and Chemical Toxicology 48 (2010) 814-819 is provided as an attachment to our submission. A prevailing question in establishing

regulatory thresholds for the major food allergens surrounds the possibility that some of the most highly sensitive individuals (as defined by dose) might not have been included in the dataset of individuals challenged. It is common practice, on grounds of patient safety to exclude patients with histories of severe reactions from clinical challenge studies, although this did not happen in the dataset analyzed in the above paper. Because of this, it was possible to analyze this study to investigate whether such exclusion would have a significant effect on reference doses that might be derived from it. This peanut dataset demonstrated, in a comparison of peanut-allergic patients with histories of severe reactions to patients with histories of less serious reactions, that no differences were observed in estimates of population threshold doses.

In 2012, ILSI Europe organized a Workshop on "Food Allergy: From Thresholds to Action Levels" in collaboration with The Food Allergy Research & Resource Program (FARRP), Health Canada's Food Directorate, ILSI North America, ILSI Japan and the University of Nebraska held on 13 to 14 September 2012 in Reading UK. The goal and purpose of the workshop was to share the work of global experts and to foster a consensus over the feasibility of defining reference values. These global experts recognized that over the last few years, considerably more low-dose challenge data have become available and tools to analyze these data and apply them to quantitative risk assessment have also continued to develop. Population dose distributions for many major regulated allergens have thus been developed and risk models elaborated to estimate the impact of defined contamination patterns within the specific population of allergic consumers.

The output of the Workshop consists of the preparation of three manuscripts, covering three major topics; a. Establishment of reference doses for food allergens in line with standard toxicological principles (i.e., NOAEL, LOAEL, referencing dose, etc.); b. Model for translating reference doses to action levels and; c. Intake data requirements for use in food allergen risk assessment. The three manuscripts are in the process of submission for publication. ILSI North America plans to submit the three manuscripts to the FDA as part of the agency's information gathering once the manuscripts have been accepted for publication.

4) **What approaches exist for using biological markers or other factors related to the severity of allergic responses in a threshold risk assessment?**

The ILSI North America Technical Committee on Food and Chemical Safety supports the Food Allergy Resource and Research Program's (FARRP) approach to focus on probabilistic risk assessment for establishing thresholds. The Committee commissioned a peanut data set that FARRP researched and published in 2010.

The manuscript, "Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals" S.L. Taylor, D.A. Moneret Vautrin, R.W.R. Crevel, D. Sheffield, M. Morisset, P. Dumont, B.C. Remington, J.L. Baumert Food and Chemical Toxicology 48 (2010) 814-819 is provided as an attachment to our submission. A prevailing question in establishing regulatory thresholds for the major food allergens surrounds the possibility that some of the most highly sensitive individuals (as defined by dose) might not have been included in the dataset of individuals challenged. It is common practice, on grounds of patient safety to exclude patients with histories of severe reactions from clinical challenge studies, although this did not happen in the dataset analyzed in the above paper. Because of this, it was possible to analyze this study to investigate whether such exclusion would have a significant effect on reference doses that might be derived from it. This peanut dataset demonstrated, in a comparison of peanut-allergic patients with histories of severe reactions to patients with histories of less serious reactions, that no differences were observed in estimates of population threshold doses.

5) **What data and information exist on dietary exposure patterns for individuals on allergen avoidance diets?**

Two sections from the Workshop Draft Report are highlighted below that are relevant to Question #5.

"The risk assessment for allergens in food focuses on a relatively small sub-population, a high proportion of which are aware of the presence of specific hazards in food that may pose a risk to them: allergens. Their patterns of food consumption might therefore differ from that of the general population.

This could affect their exposure and therefore risk, either decreasing it or increasing it depending on the product. It may be assumed, but this is yet to be confirmed, that differences in food choice will be larger than differences in the amounts of certain food products consumed by allergic and non-allergic users. In other words, allergic and non-allergic consumers of a food will consume a broadly similar amount on each eating occasion. To the best of our knowledge, no structured broad (nationwide) studies have been conducted that address this factor. Also lacking are any structured surveys into the distribution of specific allergens present by cross- contact in the general food supply, a situation made worse by the limitations of current tools. This hampers the translation of food consumption data into allergen intake data."

"Furthermore, the Action Levels were based upon a 5 g (approx. one teaspoon) serving size on the assumption that an allergic person would perceive some reaction before they proceeded to consume more of the implicated food and would therefore be protected. Clearly, many foods are consumed in quantities well above 5 g and there is therefore a need to consider consumption patterns and amounts as part of the risk assessment process. This can be accomplished using quantitative risk assessment as outlined further in this report. The VITAL program was revised in 2011 to incorporate consideration of the availability of more clinical data and the range of consumption levels for various foods."

7) **What other information or data should we consider in establishing regulatory thresholds for major food allergens?**

Allergies to foods continue to grow. The establishment of thresholds will not only remove the zero threshold that currently exists under the FALCPA, but it will improve the quality of life for the food-allergic population by providing more options within supermarkets and packaged food handling establishments while bringing back confidence in the label without compromising safety. The scientific literature and experts around the world currently support the establishment of thresholds which are protective of the vast majority of the allergic population. The recommended reference doses were developed with available data based on objective reactions and indicate that any reaction will be minor and transitory in nature and does not pose a true, food safety risk to the allergic population.

ILSI North America appreciates the opportunity to provide comments concerning this very important topic. We look forward to playing a role in the public process with the submission of scientific findings to achieve results that will benefit the health of the food allergic consumer.

Sincerely,

Eric Hentges, PhD
Executive Director
ILSI North America

WORKSHOP ON

FOOD ALLERGY: FROM THRESHOLDS TO ACTION LEVELS

ORGANISED BY ILSI EUROPE IN COLLABORATION WITH:

The Food Allergy Research & Resource Program (FARRP)
Health Canada's Food Directorate
ILSI Japan
ILSI North America
The University of Nebraska (US)

13 - 14 SEPTEMBER 2012
READING, UNITED KINGDOM

Organising Committee Members

Dr. René Crevel - Chair	Unilever	UK
Prof. Joseph Baumert	University of Nebraska - FARRP	US
Mrs. Sue Hattersley	Food Standards Agency - FSA	UK
Dr. Geert Houben	TNO Quality of Life	NL
Prof. Jonathan Hourihane	University College Cork	IE
Dr. Charlotte Madsen	Technical University of Denmark	DK
Prof. Stephen Taylor	University of Nebraska - FARRP	US
Mr. Frans Timmermans	European Anaphylaxis Taskforce & Netherlands Anafylaxis Netwerk	NL
Dr. Rachel Ward	Consultant for PepsiCo International	UK
Ms. Athanasia Baka	ILSI Europe	BE

Expert Group Members

Dr. René Crevel - Chair	Unilever	UK
Prof. Joseph Baumert	University of Nebraska - FARRP	US
Dr. Yong Joo Chung	Nestlé	CH
Ms. Magdalena Haponiuk*	European Commission - DG Health & Consumer	BE
Mrs. Sue Hattersley	Food Standards Agency - FSA	UK
Dr. Corinne Herouet-Guicheney	Bayer SAS	FR
Dr. Geert Houben	TNO Quality of Life	NL
Prof. Jonathan Hourihane	University College Cork	IE
Dr. André Knulst	University Medical Centre Utrecht	NL
Prof. Marek Kowalski	Medical University of Lodz	PL
Prof. Alfonso Lampen	Federal Institute for Risk Assessment	DE
Dr. Charlotte Madsen	Technical University of Denmark	DK
Dr. Hubert Noteborn	Dutch Food and Consumer Product Safety Authority	NL
Prof. Nikolaos Papadopoulos	University of Athens	GR
Dr. Fabrice Peladan	Danone	FR
Mrs. Frédérique Respondek	Tereos-Syral	FR
Mr. Stefan Ronsmans	Coca-Cola Europe	BE
Prof. Stephen Taylor	University of Nebraska - FARRP	US
Mr. Frans Timmermans	European Anaphylaxis Taskforce & Nederlands Anafylaxis Netwerk	NL
Dr. Rachel Ward	Consultant for PepsiCo International	UK
Prof. Margitta Worm	Charité Universitätsmedizin Berlin	DE
Ms. Athanasia Baka	ILSI Europe	BE

*Observer

List of Participants

LIST OF PARTICIPANTS

Ms. Maria Laura Acebal	Food Allergy & Anaphylaxis Network - FAAN	US
Mrs. Laura Alexandrescu	European Commission - DG Research & Innovation	BE
Dr. Helen Arrowsmith	Campden BRI	UK
Mrs. Moira Austin	Anaphylaxis Campaign	UK
Ms. Athanasia Baka	ILSI Europe	BE
Prof. Diána Bánáti	ILSI Europe	BE
Prof. Joseph Baumert	University of Nebraska - FARRP	US
Mr. Tim Betts	NT Food Technical	UK
Prof. Kirsten Beyer	Charité Universitätsmedizin Berlin	DE
Dr. Marty Blom	TNO	NL
Ms. Elisa Cavandoli	Barilla G. & R. Fratelli	IT
Dr. Chun-Han Chan	Food Standards Agency - FSA	UK
Dr. Yong Joo Chung	Nestlé	CH
Dr. René Crevel	Unilever	UK
Prof. Anthony Dubois	University Medical Center Groningen	NL
Dr. Audrey Dunn Galvin	University College Cork	IE
Dr. Anke Ehlers	Federal Institute for Risk Assessment - BfR	DE
Prof. Gerhard Eisenbrand	University of Kaiserslautern	DE
Dr. Marcel Feys	Tereos-Syral	BE
Mr. Richard Fielder	Romer Labs UK	UK
Dr. Simon Flanagan	Kraft Foods (RSSL)	UK
Dr. Mary Friel	European Food Information Council - EUFIC	BE
Ms. Gill George	PepsiCo International	UK
Dr. Samuel Godefroy	Health Canada - Food Directorate	CA
Mrs. Hazel Gowland	Allergy Action/Anaphylaxis Campaign	UK
Ms. Kirsten Grinter	Allergen Bureau Australia New Zealand & Nestlé	AU
Mr. Markus Hartwig	Red Bull	AT
Mrs. Susan Hattersley	Food Standards Agency - FSA	UK
Dr. Jason Hlywka	Kraft Foods	US
Dr. Geert Houben	TNO	NL
Prof. Jonathan Hourihane	Cork University Hospital	IE
Dr. Brett Jeffery	Mars	UK
Dr. André Knulst	University Medical Center Utrecht	NL
Dr. Brent Kobielush	General Mills	US
Mrs. Alison Kretser	ILSI North America	US
Mrs. Astrid Kruizinga	TNO	NL
Dr. Ernest Kwegyir-Afful	U.S. Food and Drug Administration - FDA	US
Prof. Alfonso Lampen	Federal Institute for Risk Assessment - BfR	DE
Dr. Stefano Luccioli	U.S. Food and Drug Administration - FDA	US
Dr. Charlotte Madsen	Technical University of Denmark	DK
Prof. Clare Mills	University of Manchester	UK
Ms. Sue O'Hagan	PepsiCo Europe	UK
Dr. Patrick O'Mahony	Food Safety Authority of Ireland	IE
Dr. Alexandra Papadopoulos	French Agency for Food, Environmental and Occupational Health & Safety - ANSES	FR
Dr. Fabrice Peladan	Danone	FR
Mrs. Elaine Peters	NT Food Technical	UK
Dr. Bert Popping	Eurofins	UK
Dr. Bizhan Pourkomailian	McDonald's Europe	UK
Mrs. Lynne Regent	Anaphylaxis Campaign	UK
Dr. Mareike Richter	R-Biopharm	DE
Mr. Stefan Ronsmans	Coca-Cola Europe	BE
Ms. Maria Saïd	Anaphylaxis Australia	AU
Mrs. Sabine Schnadt	German Allergy and Asthma Association - DAAB	DE
Mrs. Anneke Sellis	Ministry of Health, Welfare and Sport	NL
Mr. Ryo Shimojo	Kikkoman Foods Europe	NL

Dr. Masahiro Shoji	Morinaga Institute of Biological Science	JP
Dr. Daniel Skrypec	Kraft Foods	US
Dr. Inge Stoelhorst	Ministry of Health, Welfare and Sport	NL
Mrs. Soultana Tatsika	EFET	GR
Prof. Stephen Taylor	University of Nebraska - FARRP	US
Mr. Frans Timmermans	European Anaphylaxis Taskforce & Netherlands Anafylaxis Netwerk	NL
Mr. Olivier Tranquet	French National Institute for Agricultural Research - INRA	FR
Dr. Carina Venter	University of Portsmouth	UK
Dr. Rachel Ward	Consultant for PepsiCo International	UK
Mrs. Liz Woolner	Unilever	UK
Dr. Ryuji Yamaguchi	ILSI Japan	JP

ILSI Europe Secretariat

Ms. Toula Aslanidis	ILSI Europe	BE
Ms. Ruth Marquet	ILSI Europe	BE

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Workshop Report

Application of scientific criteria to food allergens of public health importance ☆

Y.J. Chung [a], S. Ronsmans [b], R.W.R. Crevel [c], G.F. Houben [d], R.J. Rona [e], R. Ward [f,1], A. Baka [g,*]

[a] Nestlé Research Centre, Lausanne, Switzerland
[b] Coca-Cola Services, Brussels, Belgium
[c] Safety and Environmental Assurance Centre, Unilever, Colworth House, Sharnbrook, Bedford, UK
[d] The Netherlands Organisation for Applied Scientific Research TNO, Zeist, The Netherlands
[e] King's College London, Department of Psychological Medicine London, UK
[f] PepsiCo International, UK
[g] International Life Sciences Institute – ILSI Europe, Brussels, Belgium

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ABSTRACT

Scientific criteria for identifying allergenic foods of public health importance (Björkstén, B., Crevel, R., Hischenhuber, C., Løvik, M., Samuels, F., Strobel, S., Taylor, S.L., Wal, J.-M., Ward, R., 2008. Criteria for identifying allergenic foods of public health importance. Regulatory Toxicology and Pharmacology 51(1), 42–52) have been further refined to incorporate an assessment of the strength of available scientific evidence (van Bilsen, J.H., Ronsmans, S., Crevel, R.W., Rona, R.J., Przyrembel, H., Penninks, A.H., Contor, L., Houben, G.F., 2011. Evaluation of scientific criteria for identifying allergenic food of public health importance. Regulatory Toxicology and Pharmacology 60, 281–289). A multi-disciplinary group was invited to critically test the refined approach. They independently evaluated selected publications on coconut, soy and/or peanut allergy, scored them using the newly developed level of evidence criteria, and debated proposed approaches for combining and utilising the scores to measure the overall impact of an allergen in public health impact assessments. The evaluation of selected publications using the modified criteria produced a relatively consistent result across the experts. These refined criteria were judged to be a way forward for the identification of allergenic foods of public health importance, and for prioritisation of allergen risk management and future data gathering. The debate to combine available evidence when assessing whether an allergenic food is of sufficient public health importance to warrant active management led to proposals on how to weight and combine evidence on allergen severity, potency and prevalence. The refined criteria facilitate a debate to find a meaningful sequence of steps to summarise the available information in relation to a food allergen.

1. Introduction

Food allergy has been recognised by food safety authorities as a public health concern. In 1995 at the time the list of the most common allergenic foods was drawn up by the World Health Organization (WHO) (FAO 1995; Codex, 1999), information on prevalence and severity was used, but available data was very limited. Since then, well-documented cases of allergic reactions to numerous allergenic foods have been reported, (FAO, 1995; Hefle, Nordlee, and Taylor, 1996; Taylor, 2000; EFSA, 2004; Burks et al., in press). Food allergen labelling lists currently vary widely across the globe (Gendel, 2012), usually based on the Codex list (Codex, 1999). Addition of allergenic foods to local labelling lists does not follow a harmonised approach in risk assessment and risk management decision-making, leading to confusion, and practical challenges for industry, consumers and public health agencies alike. Allergic consumers require appropriate and accurate risk communication of the allergenic potential of a given food to make sound judgments about avoiding foods to which they are sensitised (Sakellariou

ILSI Europe International Life Sciences Institute

Commissioned by the ILSI Europe Food Allergy Task Force

Abbreviations: DBPCFC, double blind placebo-controlled food challenge; ED 50, eliciting dose 50; FAO, Food and Agriculture Organisation; FARRP, Food Allergy Research and Resource Programme; IgE, immunoglobulin E; ILSI, International Life Sciences Institute; IUIS, International Union of Immunological Societies; JEFCA, The Joint FAO/WHO Committee on Food Additives; LOAEL, lowest-observed-adverse-effect-level; SBPCFC, single-blind, placebo-controlled food challenge; SPT, skin prick test; WHO, World Health Organisation.

☆ Proceedings of a Mini-Workshop held on 16–17 September 2010, in Brussels, Belgium. Organised by ILSI Europe.

* Corresponding author. Address: ILSI Europe a.i.s.b.l., Avenue E. Mounier 83, Box 6, 1200 Brussels, Belgium. Fax: +32 2 762 00 44.
E-mail address: publications@ilsieurope.be (A. Baka).
[1] Present address: R. Ward Consultancy Limited, Nottingham, UK.

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et al., 2009; Barnett et al., 2011). Use of explicit scientific criteria to justify addition of foods to allergen lists would ensure public health protection measures are pertinent to local needs and protect allergic consumers.

In order to decide objectively if a food needs to be addressed as an allergenic food of public health importance, three questions have to be answered: Is the food allergenic? Is its allergenicity of public health significance? What is the quality of the data available to answer the previous two questions? With these questions in mind, an expert group appointed by the ILSI Europe Food Allergy Task Force proposed a set of scientific criteria together with a framework for their use (Björkstén et al., 2008). These criteria included clinical characterization (IgE-mediated reaction), potency of the allergen, severity of the reaction and prevalence in a population. In the framework, the quality of the evidence supporting each of these criteria in the available dataset (body of scientific literature) is assessed using a score that had been developed by discussion and consensus by an expert committee. Such criteria can be useful in making a decision as to whether sufficient quality data exist to evaluate individual allergenic foods regarding their level of public health significance. If so, the criteria can serve as a common basis for assessing and comparing the public health impact of allergens. If the criteria indicate that quality data are lacking, they have the benefit of pointing out the direction in which more research is needed to be able to perform proper risk assessments. Efforts have been made elsewhere to develop objective criteria for the establishment of allergenic foods as a priority for public health, notably by Health Canada (Health Canada, 2010). An example of applying these criteria was the recent evaluation by Health Canada of mustard and garlic, resulting in only mustard having been added to the Canadian priority food allergen list (Health Canada, 2009a,b; Health Canada, 2010).

Further refinement of the original scientific criteria developed by Björkstén et al., 2008) has been performed recently (van Bilsen et al., 2011). A partnership between ILSI Europe and TNO aimed to test and review the application of the proposed criteria (Björkstén et al., 2008) to assess whether this approach could be widely used, and to further evaluate whether the criterion and the descriptors for the quality of evidence were unambiguous and covered the full range of type and levels of evidence in the literature. The resulting refinement of the descriptors provided guidance on how to interpret the literature in terms of strength of the evidence and demonstrated that the criteria framework could discriminate between high, moderate and low quality of evidence. It also reaffirmed the benefits of having objective scientific criteria in a structured framework to support a harmonised and consistent scientific approach, and thus provides an explicit basis for future assessments of allergenic foods to risk assessors and risk managers with a varied range of experience of food allergy. While this framework establishes a common basis regarding the scientific evidence to be included in an allergens risk assessment exercise, it does not provide an actual evaluation of the public health relevance of that allergen.

In practice, public health assessments always have to use the data available at the time. As such, using this framework allows for assessing the available information taking into account its quality, and provides the basis for carrying out a systematic review of the evidence regarding a specific allergen. Performing such assessments on a set of known and potentially new allergens, will allow identification of data gaps in science, if any. Subsequently such assessments allow for an exercise in prioritisation according to relevance for public health, comparing food allergens relative to each other. The relevant parameters for doing so are prevalence in the local population, potency of the allergen and severity of adverse reactions.

The ILSI Europe Food Allergy Task Force organised a workshop in September 2010 primarily to further assess the applicability, completeness and ease of use of the approach. A range of potential users of the scientific criteria framework (i.e. government risk assessors and risk managers, regulators, public health scientists, industry risk managers) not involved in the development of the criteria were invited to the workshop. The experts were asked to undertake an independent evaluation of selected scientific publications on several foods using the scientific criteria developed and refined (Björkstén et al., 2008; van Bilsen et al., 2011). In other words, the usability and value of these criteria were assessed on data on several foods.

Having invited a great variety of experts to the workshop for validating the applicability of the proposed criteria for the evaluation of the strength of scientific evidence, the workshop also performed an initial brainstorming exercise, on how one could approach an assessment of public health impact of existing and emerging allergens. Based on the feedback received, this report contains suggestions that will be useful to initiate further work in that area. This paper presents the process, outcome and recommendations emerging during the workshop.

2. Workshop methodology approach

2.1. Application of the modified criteria to a selected set of scientific publications

The first element of the workshop review was to examine how consistently the modified criteria and quality of descriptors (van Bilsen et al., 2011) could be applied to a selection of food items as reported in the scientific literature. Scientific papers on three known or emerging allergenic foods (peanut, coconut and soybean) were chosen by the Expert Group for this exercise. Peanut was chosen as the initial case study for evaluation as a well-known and broadly investigated allergen, with documented severe reactions at low doses. Two further and contrasting examples were chosen for the workshop evaluation – soy as an allergen with much higher thresholds for elicitation of adverse reactions, and coconut as a potential emerging allergen. The scientific papers were sourced from the scientific literature database developed in the previous work done by the expert group and TNO, utilising the Food Allergy Research and Resource Program (FARRP, University of Nebraska) database on allergenic foods, and the US National Library of Medicine's Medline service, using prescribed search keywords as described in van Bilsen et al. (2011). The publications provided for review for each allergen are listed in the Appendix.

Scientific experts were invited from different stakeholder groups, (i.e. food industry, governments, academia, research organization, and consumer protection), and from a wide range of scientific fields, (e.g. clinicians, biochemists, toxicologists, food scientists, epidemiologists, public health scientists). A list of the participants can be found on www.ilsi.eu. Each invited scientist was asked to assess and score the quality (strength) of evidence for a set of scientific papers for each of two out of three chosen allergenic foods (peanut, soy and/or coconut) using the defined criteria, and scoring them against the modified descriptors for levels of evidence (see Table 1). Each individual's findings were first combined and discussed in a single small group of 8–9 participants. After completing the scoring for quality of evidence for each criterion, the groups then shared their evaluations with a second group evaluating the same papers for the same allergenic food to compare consistency in scoring, highlight any ambiguity in interpretation and identify potential improvements/refinements. Each workgroup was represented by the experts in various fields. This review mechanic was felt to provide a practical test of the robustness, ease of use and clarity of the criteria and their descriptors for assessing level of evidence.

Table 1
Type and level (weight) of evidence of clinical data according to modified criteria – text in bold are the modifications described in van Bilsen et al. (2011) made to the original criteria described in Björkstén et al. (2008).

Data supporting	Type of evidence	Level of evidence
IgE-mediated mechanism	At least two studies **from independent centres, each based on at least one patient, in which** the patient samples and food proteins are well defined[a], demonstrating the presence of bound IgE antibodies and/or a positive SPT[b]	1
	At least two studies **from independent centres, each based on at least one patient, in which the patient samples and food proteins are not well defined, demonstrating the presence of bound IgE antibodies and/or a positive SPT**[b]	2
	At least two serological studies showing specific IgE binding to foods/extracts and/or a positive SPT	3
	At least two studies of small numbers of serum samples from patients who are not adequately characterised	4
Adverse reactions caused by IgE-mediated mechanisms	DBPCFC[c,d] studies in well-characterised patients with defined doses of specific food[a] in well-described matrix[e] and with specific bound IgE antibodies and/or a positive SPT	1
	Series of patients with well-documented[a] history of reactions to suspected food, confirmed or not by DBPCFC[c], and with specific bound IgE antibodies and/or a positive SPT	2
	Case reports of clinical symptoms and the presence of food-specific bound IgE antibodies and/or a positive SPT, but not confirmed by DBPCFC	3
	Elimination diets leading to resolution of symptoms	4
Potency	One or more threshold studies with good range of doses[f] and adequate numbers of **unselected** participants with documented clinical symptoms of allergy. Two or more level 2 threshold studies could add up to level 1	1
	Other threshold studies	2
	Case reports describing reactions to quantitatively estimated low doses	2
	Case reports describing reactions to qualitatively estimated low doses	3
Severity	Objective signs confirmed by physician, preferably classified according to scientifically accepted classification system	1
	Subjective symptoms reported by patient in DBPCFC study for repeated doses	2
	Subjective signs reported by patient in DPBCFC study at single dose	3
	Historical symptoms indicated by patient	4
Prevalence	Epidemiological studies in general community population, including verification of sensitization by IgE antibodies or positive SPT, presence of clinical symptoms and DBPCFC[d]	1
	As above but without DBPCFC[d]	2
	Epidemiological studies based on questionnaires for clinical symptoms and sensitization in the general population	2
	Epidemiological studies based on questionnaires for clinical symptoms or sensitization in the general population	3
	Surveys based on general clinics patients (e.g. general practitioners, children clinics)	4
	Registers of severe allergic reactions	4

[a] Level of details sufficient to be reproducible.
[b] Skin prick test, preferably performed according to the accepted Guidelines.
[c] Double-blind placebo-controlled food challenge.
[d] Or open challenges for infants.
[e] Matrix with appropriate placebo control (with identical matrix composition as the matrix of active allergic material).
[f] Dose-spacing should consist of doubling doses or involve a semi-logarithmic progression, starting at a dose low enough not to provoke a reaction in any participant. Moreover, no effect and effect level of clinical signs should be included.

2.2. Application of the findings in a public health impact assessment exercise

The second element of the workshop was to brainstorm and offer initial ideas on how the different scientific criteria, with varying strength of supporting evidence, could be incorporated into an overall assessment of the public health relevance of existing and emerging allergens. In order to facilitate the discussions, three different approaches were shared for critique at the workshop. The groups were asked to discuss the pros and cons for one option each, and, if possible, recommend additional options explaining the reasoning for a particular approach to a plenary feedback session.

3. Results

3.1. Application of the modified criteria to a selected set of scientific publications for coconut, soy and peanut

The workshop participants examined how consistently the modified criteria and quality of evidence descriptors developed by ILSI Europe (Table 1; Björkstén et al., 2008; van Bilsen et al., 2011) could be applied to a selected dataset from the scientific literature. The results from individual assessments and group scores for each allergenic food considered are combined in Table 2 to describe the overall quality of evidence for each criterion provided by the scientific papers reviewed by the groups for all three allergenic foods. The evaluation of selected publications using the modified criteria produced a satisfactory degree of consistency across the experts. However, a few specific differences did arise in interpretation of the descriptors when scoring quality and weight of evidence for IgE-mediated hypersensitivity reactions.

Following review of a set of eight papers on coconut, it was concluded that evidence for IgE-mediated allergic reactions existed for coconut allergy, but data on prevalence and potency were lacking. Based on this dataset, more research appeared necessary, especially regarding data on prevalence. In discussion, the participants noticed that the discrepancy in the conclusions on the criterion of IgE-mediated mechanism as indicated in Table 2 (footnotes (a) and (b)) and Table 3 resulted from different interpretations of the relevant papers about the number of serum samples from patients. After discussion on the number of samples required to fulfil the cri-

Table 2
Summary of the overall level of agreement between groups on the level of quality of evidence of scientific publications.

Criteria	Level of quality of evidence					
	Coconut		Soybean		Peanut	
	Group 1	Group 2	Group 2	Group 3	Group 1	Group 3
IgE-mediated mechanism	1[a]	3[b]	2	1	2	1
Adverse reaction with IgE-mediated reaction	3	3	1	1	1	1
Potency	3	3	1	1	2	1
Severity	1	1	1	1	1	1
Prevalence	4[c]	Not ranked[d]	Not ranked[d]	Not ranked[d]	2	2

[a] At least two studies, in which the patient samples and food proteins are well defined, demonstrating the presence of bound IgE antibodies and/or a positive SPT.
[b] At least two studies of small numbers of serum samples from patients who are not adequately characterised.
[c] Registers of severe allergic reactions.
[d] Due to inapplicability of criteria to the data described in papers.

Table 3
Details of the evaluations of scientific papers on coconut allergy.

Criteria	Rank	Papers evaluated																	
		1		2		3		4		5		6		7		8		Overall rank	
		G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2	G1	G2
IgE	1	x										x						x	
	2																x		
	3		x			x	x	x	x				x			x			x
Adverse reaction	1																		
	2																		
	3	x	x			x	x	x	x			x	x			x		x	x
	4																		
Potency	1																		
	2																		
	3						x		x			x						x	x
Severity	1	x	x			x	x											x	x
	2																		
	3																		
	4																		
Prevalence	1																		
	2																		
	3																		
	4	x														x		x	

G1, group 1; G2, group 2; x denotes the level of quality of evidence agreed by the group assessing the evidence provided, where 1 is highest quality of evidence and 4 is the least (see Table 1).
Where a column is blank, the group found the information provided was insufficient to classify the quality of evidence.

terion for an IgE-mediated mechanism, it was concluded that the description "a small number of serum samples" for a level 3 quality of evidence was vague and that the number should be refined to state "serological studies with at least five samples" as the criteria to list a protein as an allergen (Champman et al., 2007). The discrepancy in the conclusion on the criterion of prevalence, as indicated in Table 2 (footnotes (c) and (d)), resulted from the fact that group 1 considered a case report to be a registered severe allergic reaction whereas group 2 interpreted a case study as being a single case, which was not classifiable by the modified criteria. In any event, both groups identified that there was inadequate data to assess prevalence. Scoring of the quality of evidence provided by single case studies was also discussed. Although participants agreed that serological analyses made in single case studies could be of excellent quality, they could not be scored as level 1 for the purposes of establishing an IgE-mediated mechanism, as they had, by definition, not been reproduced. Such high-quality studies, however, are important in identifying emerging or new allergens. The allergenicity of a large number of foods is supported only by serological evidence such as cross-reactivity, identification of IgE binding proteins, and/or skin prick tests, without oral challenge studies. Although single oral challenge case studies can, by their nature, provide only limited data on prevalence, they can serve as useful signals and are therefore meaningful in identifying emerging allergens.

The evaluation of the pre-selected articles on soy allergy is described in Table 4. The conclusions of both groups were similar overall, with a difference in scoring on the IgE-mediated mechanism resulting from the different interpretation of each group regarding the number of qualifying studies. One group ranked the criterion on IgE-mediated mechanism as a level 2, based on their finding that only one of the supplied studies qualified as a level 1. The other group ranked the IgE criterion as a level 1, having concluded that more than one study qualified for a level 1 score. As a consequence, a discussion on the quality and quantity of the evaluated studies took place. One group took the approach that in a literature set in which only one study qualifies for a level 1 (and several other studies classify as sub-level 1), a resulting level 2 should be the conclusion. On the other hand, the other group classified two out of five studies as level 1 and therefore concluded that the same data warranted a final level 1 score. The different interpretations led the participants to recognise a need for harmonisation in determining final scores for the IgE criteria when combining the conclusions on several studies, if each individual study gave a different conclusion in terms of strength of evidence. It should be noted that this remark is also a result of the design

Table 4
Details of the evaluations of scientific papers on soybean allergy.

Criteria	Rank	Papers evaluated											
		1		2		3		4		5		Overall rank	
		G2	G3	G2	G3	G2	G3	G2	G3	G2	G3	G2	G3
IgE	1		X							X	X		X
	2	X										X	
	3			X		X							
Adverse reaction	1	X								X	X	X	X
	2		X										
	3					X							
	4												
Potency	1									X	X	X	X
	2		X				X						
	3												
Severity	1	X	X			X	X		X	X	X	X	X
	2												
	3												
	4												
Prevalence	1												
	2												
	3												
	4											nr*	nr*

G2, group 2; G3, group 3; x denotes the level of quality of evidence agreed by the group assessing the evidence provided, where 1 is highest quality of evidence and 4 is the least (see Table 1).
Where a column is blank, the group found the information provided was insufficient to classify the quality of evidence.
* nr, not ranked.

Table 5
Details of the evaluations of scientific papers on peanut allergy.

Criteria	Rank	Papers evaluated									
		1		2		3		4		Overall rank	
		G1	G3	G1	G3	G1	G3	G1	G3	G1	G3
IgE	1			X	X		X				X
	2	X				X				X	
	3		X								
Adverse reaction	1			X	X					X	X
	2						X				
	3										
	4										
Potency	1				X						X
	2			X						X	
	3										
Severity	1			X	X					X	X
	2										
	3						X		X		
	4							X			
Prevalence	1										
	2					X			X	X	X
	3										
	4										

G1, group 1; G3, group 3; x denotes the level of quality of evidence agreed by the group assessing the evidence provided, where 1 is highest quality of evidence and 4 is the least (see Table 1).
Where a column is blank, the group found the information provided was insufficient to classify the quality of evidence.

and context of the exercise, whereby only a few papers were provided to individual assessors.

The details and overall scoring of criteria for four selected articles on peanut allergy are shown in Table 5. Some discrepancies in the conclusions surfaced between assessors. Evaluation of the criteria for IgE-mediated mechanisms showed that one of the articles had data on a skin prick test using peanut protein extract. However, the source of the protein extract was not described in the article. In order for skin prick test (SPT) data to be credible, the source of protein extracts should be indicated in the papers and proteins from commercial sources would be sufficient for reproducibility of the procedure. It was suggested that for the criteria on evidence for severity, subjective symptoms should be left out of the criteria of level 3 of evidence, as they are already considered level 2 of evidence. In addition, the importance of number of doses in the DBPCFC study was questioned, suggesting omission of the number (single or repeated) of doses from the descriptors of level 2 and 3 evidence. Only one out of the four studies on peanut allergy was suitable for assessing evidence of potency (i.e. how much is needed to trigger a reaction). For this study, the two groups ranked the evidence differently. The discrepancy arose from the interpretation of the number of studies. Whereas one group interpreted the study by

Hourihane et al. (2005) to involve two centres in two different studies, the other group considered the study by Hourihane et al. (2005) to be a single study in one centre. As a consequence, the first group attributed a top level 1 score to the study, whereas the second group ranked it at a level 2 with respect to the quality of evidence for this criterion. During the discussion, participants concluded that clarification was needed as to how to deal with the number of centres when scoring the quality of evidence for the criterion of potency. For example, the study by Hourihane et al. (2005) included several clinics that recruited allergic patients and one centre for food challenge studies. A minor modification of the descriptor for level 1 evidence for the potency criterion might be necessary to clarify the actual meaning of "at least two centres" in one study or one publication.

Besides the individual remarks made on the fine-tuning of the modified Björkstén et al. (2008) criteria by the groups, it was also proposed that in order to ensure applicability of the overall set of criteria, the criteria should be kept as simple and concise as possible. Usability of the criteria for risk assessors and managers in the food industry and government authorities needs to be kept in mind. It was concluded that a balance should be achieved between including too much detail in order to cover all possible scenarios and a lack of detail in the descriptors of the scoring which would not be able to capture the appropriate level of quality of evidence.

3.2. Approaches for utilising the criteria and strength of evidence for each element in an overall public health impact assessment

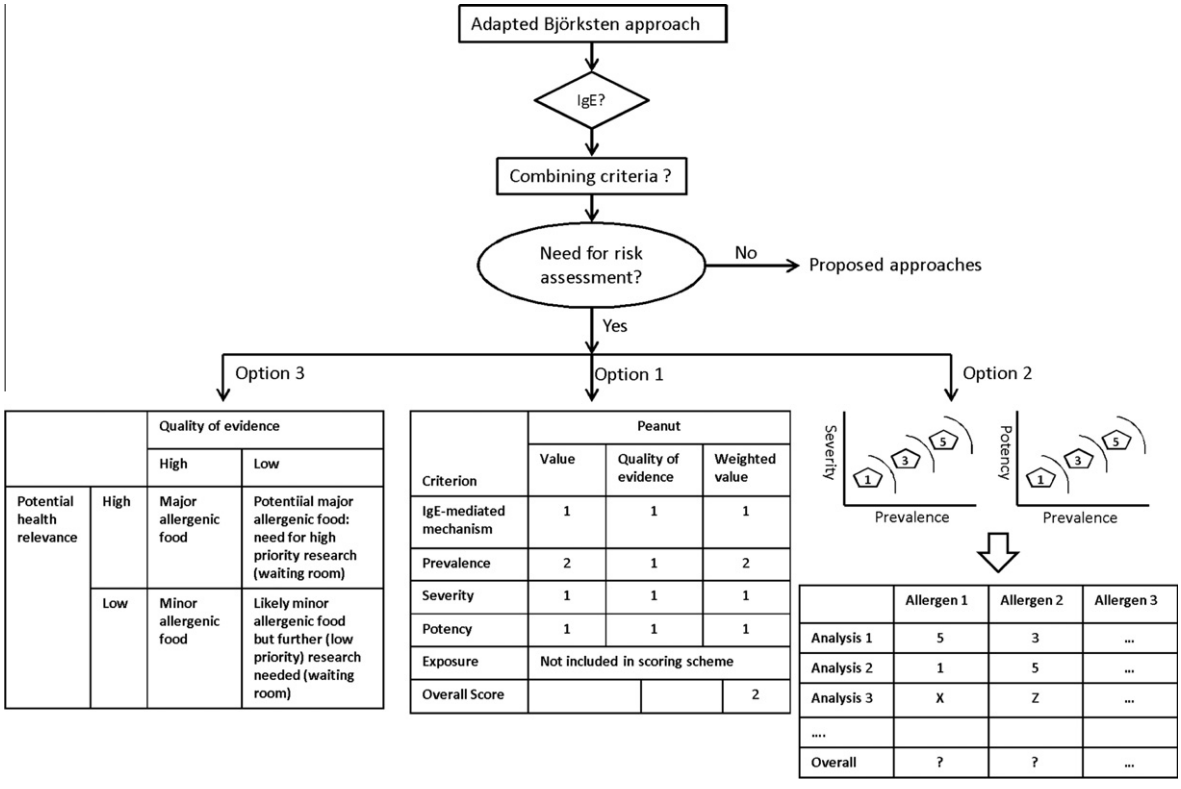
Following the evaluation of example papers on individual allergenic foods to identify the quality and weight of evidence of IgE-mediated allergy, the groups went onto explore how risk managers could ascertain whether the evidence available could be used to (i) indicate the overall public health importance of a food allergen in contrast to its importance to the health of individuals with the allergy (e.g. risk of adverse reactions to a specific food), and (ii) discriminate between the impact of different allergenic foods on public health.

Three initial options were provided to prompt the brain-storming session:

Option 1: A weighted value approach. This approach aimed to capture and quantify for a given allergen, for each individual criterion, the combination of the strength of evidence that exists for this criterion and the actual level of findings (e.g. low versus high prevalence) that can be concluded upon for that criterion. To use this approach, one would need to develop a grading system to classify the level of findings for the different criteria. The strength of the scientific literature would follow from the modified Björksten et al. classification. The overall final combined numerical score would be a possible way of prioritising allergens versus each other.

Option 2: A group analysis approach. This approach sought to map out two-dimensional charts, with the aim of comparing the prevalence in relation to the potency and severity of a given allergen respectively. Each allergen could then be positioned in one of the chart areas as a function of the two criteria being evaluated. By grading the domains of the chart in such a way, one can visualise the difference between several allergens, or one can use the numerical values attributed to the different chart areas. Both option 1 and option 2 approaches could be measures of the relative public health relevance of allergens.

Option 3: A high versus low priority approach. This approach simply ranks both the quality of evidence as well as the potential health relevance, as a qualitative descriptor: high or low. This simple approach could be valuable in a top-line prioritisation exercise, where one seeks to identify the priority allergens to



		Quality of evidence	
		High	Low
Potential health relevance	High	Major allergenic food	Potentiial major allergenic food: need for high priority research (waiting room)
	Low	Minor allergenic food	Likely minor allergenic food but further (low priority) research needed (waiting room)

Criterion	Peanut		
	Value	Quality of evidence	Weighted value
IgE-mediated mechanism	1	1	1
Prevalence	2	1	2
Severity	1	1	1
Potency	1	1	1
Exposure	Not included in scoring scheme		
Overall Score			2

	Allergen 1	Allergen 2	Allergen 3
Analysis 1	5	3	...
Analysis 2	1	5	...
Analysis 3	X	Z	...
....			
Overall	?	?	...

Fig. 1. Diagram illustrating options considered for public health impact assessment of allergenic foods.

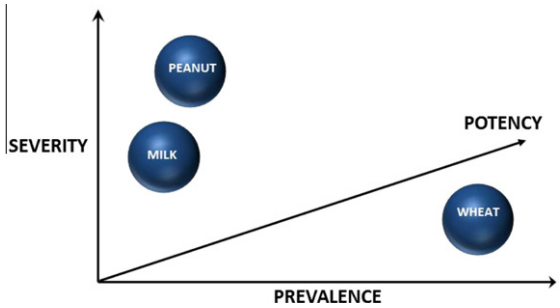


Fig. 2. Diagram illustrating the potential for three-dimensional relative positioning of allergenic foods against the three key criteria of potency, severity and prevalence.

work on, versus the ones that can be considered to be in the "waiting room" in terms of insufficient evidence, further research or regulatory measures. A schematic representation of the thinking behind each option is depicted in Fig. 1.

Combining the weighted value approach (option 1) and group analysis approach (option 2) was suggested as one way to express this evidence of likelihood of severe adverse reactions in such a way that it can discriminate between different foods of proven allergenicity (Fig. 2). Numerical scoring to rank individual allergenic foods was not viewed as feasible, given the disparate types of data, limited evidence usually available, and the uncertainty as to whether future studies would be able to cater for the missing gaps (either due to lack of funding or lack of sufficient allergic subjects available for challenge tests). Risk managers, however, still need to make decisions on public health importance using whatever data they have available. The group therefore tried to develop an alternative approach that would permit best use of any/all data available on known and future/emerging allergenic foods. Ideally, the approach would also permit observation of the impact of any changes over time.

The weighted value approach (option 1) combines quality of evidence and the "magnitude" of the findings themselves. It allows transparency of data used for decision making, however, the current scores describe levels of evidence and not level of public health concern. Thus, any number generated should be seen as an aid to decision making and not a definitive or comparative "score" for the impact of an allergenic food on public health. The group analysis approach (option 2) provided helpful visual representation of the impact of the criteria and could show how allergens were positioned relative to each other, but would not illustrate strength of evidence. The high versus low priority approach (option 3), may need more choices in scale to better translate the ILSI scientific criteria approach. In general, each option has its own merits and can complement the others. However, some participants were sceptical of the merits of any of these approaches.

To create a benchmark, data presentation using three-dimensional plots against prevalence, potency and severity was suggested for the existing regulated allergenic foods. A peanut allergy index of risk potential was suggested that could be used as the reference food item and other allergenic foods could be compared relative to this referent. Clustering could further provide additional information of impact due to any/all of the three vectors. Different populations and even potential at-risk subpopulations (e.g. those on restricted diets, such as vegetarians and diabetics) could be compared with the general population. Data gaps could then help identify areas for improvement in clinical and epidemiological data collection for food allergy public health decision making. The impact on quality of life in allergic patients' also needs to be considered in the assessment and included into the criteria. Combining criteria to derive a single estimate of public health impact has the potential to disregard important information Thus decision making should not rely only on one summary estimate.

Further thinking in this area is needed and a new ILSI Europe expert group will continue to progress approaches for public health impact assessments for food allergens.

4. Discussion and conclusions

The workshop participants concluded that the modified criteria with the associated quality descriptors and scores for levels of evidence developed by ILSI Europe (Björkstén et al., 2008; van Bilsen et al., 2011), provide a practical approach for assessing the strength of evidence supporting the classification of food allergens. The assessment of scientific papers exercise was also felt to be practical and gave structure to a valuable discussion on assessing quality of evidence. The descriptors were judged to be helpful in determining the weight that should be accorded to each element of the available evidence.

The evaluation of selected publications for their weight of evidence according to the modified criteria based on the paper by Björkstén et al. (2008) was relatively consistent between groups of experts. Minor modifications in descriptors of the quality of evidence for each of the criteria would improve coherent application by users, such as clarifying the required number of serum samples for patients and guidance on interpretation of number of studies and number of centres. In addition, incorporation of inclusion criteria for eligible publications, as used by Health Canada for inclusion of new allergenic foods to their food allergen list was acknowledged as an existing precedent (Health Canada, The Canadian Criteria for the Establishment of New Priority Food Allergens, 2010).

The exercise demonstrated that agreement between experts is possible, but minor differences between assessors will remain due to type of expertise and variation in the ability to appraise the literature of food allergy. The structure of the ILSI Europe scientific criteria allows the use of all available data, but information for many (especially emerging) allergens is scarce and often of limited quality. The structure also allows identification of critical gaps in data for identifying allergenic foods of public health importance. Resources can then be allocated in the most effective way to address these data gaps.

The workshop confirmed that the three key criteria to establish the public health importance of an allergenic food would be potency, severity and prevalence.

- Potency could be preferably expressed as the ED50 (amount required to produce a reaction in 50% of a specific allergic population) or ED10 of the Minimum Eliciting Dose distribution or, if not available, the LOAEL (lowest observed adverse effect level). Differentiation according to type of effect is possible. Categorisation (allergens allocated in, e.g. low, medium or high potency categories) is also possible, but decisions on cut-offs are needed for that. Categorisation, if preferred, will be done later in the hazard assessment process because the expression of potency as a value gives more information.
- Severity of effects should be indicated in combination with their frequency in the population. Categorisation is possible as minor, moderate or severe, however further development of definitions would be needed. It was suggested that severity be expressed as incidence (%) of effects in a population.
- Prevalence of allergy can vary geographically and these differences should be listed as part of the hazard characterisation. It is a risk management decision whether or not to use the high-

est prevalence in any region. Patient recruitment and selection issues are possible. Prevalence is preferably expressed as the absolute prevalence in a population or as the relative (%) prevalence among food allergy patients.

It was recommended that potency, severity and prevalence as criteria should *not* be dealt with via a decision tree approach where conclusion on one criterion would determine whether another criterion is to be considered, but that all three criteria should be considered in a weight-of-evidence approach. A high prevalence of mild effects might, for instance, be as important as a very low prevalence of moderate/severe effects. Instead, a three-dimensional positioning of allergens could be used to illustrate the impact of different allergens relative to each other. Fig. 2 visually represents how this might be done. A critical consideration in combining data from different sources to determine the public health importance of an allergenic food is what weight (by importance) to attribute to each component. In this context, it is difficult to do this unless the risk management objectives are clearly set out first. In a societal context for example, does a very large number of fairly mild reactions count for the same as a few severe, life-threatening ones?

These refined criteria were judged to represent an improvement and be a way forward as an expert tool for the identification of food allergens of public health importance, and for prioritisation of allergen risk management and future data gathering. A full application of the modified (or simplified) quality of evidence descriptors to the literature on a known allergen would ensure the value of such criteria in risk assessment. Future work should now be done to apply and incorporate this scientific criteria framework into an overall weighted approach of establishing the actual public health importance of a given allergen.

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14.

The opinions expressed herein and the conclusions of this publication are those of the authors based on the discussions with those attending the workshop and do not necessarily represent the views of ILSI Europe nor those of its member companies.

Appendix A. List of literature provided for each allergen

Coconut. allergy

Nguyen et al. (2004). Cross-reactivity between coconut and hazelnut proteins in a patient with coconut anaphylaxis. Annals of Allergy, Asthma and Immunology 92(2), 281–284.

Fiocchi et al. (2006). Food allergy and the introduction of solid foods to infants: a consensus document. Annals of Allergy, Asthma and Immunology 97(1), 10–21.

Rosado et al. (2002). Anaphylaxis to coconut. Allergy: European Journal of Allergy and Clinical Immunology 57(2), 182–183.

Tella et al. (2003). A case of coconut allergy. Allergy: European Journal of Allergy and Clinical Immunology 58(8), 825–826.

Burks et al. (2001). Food allergens. Current Opinion in Allergy and Clinical Immunology, 1(3), 243–248.

Teuber and Peterson (1999). Systemic allergic reaction to coconut (*Cocos nucifera*) in 2 subjects with hypersensitivity to tree nut and demonstration of cross-reactivity to legumin-like seed storage proteins: New coconut and walnut food allergens. Journal of Allergy and Clinical Immunology 103(6), 118

Sicherer et al. (2003). Prevalence of peanut and tree nut allergy in the United States determined by means of a random digit dial telephone survey: a 5-year follow-up study. Journal of Allergy and Clinical Immunology 112(6), 1203–1207.

Rangsithienchai et al. (2009). Prevalence of coconut allergy in children with tree nut and peanut allergies. Journal of Allergy and Clinical Immunology 123, S26 (Abstract).

Soy. allergy

Bruno et al. (1997). Soy allergy is not common in atopic children: a multicenter study. Paediatric Allergy and Immunology 8(4), 190–193.

Codina et al. (2003). Allergenicity of varieties of soybean. Allergy: European Journal of Allergy and Clinical Immunology 58(12), 1293–1298.

Foucard and Malmheden Yman (1999). A study on severe food reactions in Sweden – is soy protein an underestimated cause of food anaphylaxis? Allergy: European Journal of Allergy and Clinical Immunology 54(3), 261–265.

Heine et al. (2006). Proposal for a standardized interpretation of the atopy patch test in children with atopic dermatitis and suspected food allergy. Pediatric Allergy and Immunology 17(3), 213–217.

Ballmer-Weber et al. (2007). Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. Journal of Allergy and Clinical Immunology 119(6), 1489–1496.

Peanut allergy

Chung and Champagne (1999). Allergenicity of Maillard reaction products from peanut proteins. Journal of Agricultural and Food Chemistry 47(12), 5227–5231.

Hourihane et al. (2005). Does severity of low-dose, double-blind, placebo-controlled food challenges reflect severity of allergic reactions to peanut in the community? Clinical and Experimental Allergy 35(9), 1227–1233.

Tariq et al. (1996). Cohort study of peanut and tree nut sensitisation by age of 4 years. British Medical Journal 313(7056), 514–517.

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Evaluation of scientific criteria for identifying allergenic foods of public health importance

J.H.M. van Bilsen [a,*], S. Ronsmans [b], R.W.R. Crevel [c], R.J. Rona [d], H. Przyrembel [f], A.H. Penninks [h], L. Contor [e], G.F. Houben [g]

[a] TNO Earth Environmental and Life Sciences, Zeist, The Netherlands
[b] Coca-Cola Services, Brussels, Belgium
[c] Safety and Environmental Assurance Centre, Unilever, Colworth House, Sharnbrook, Bedford, UK
[d] King's College London, Department of Psychological Medicine London, UK
[e] International Life Sciences Institute – ILSI Europe, Brussels, Belgium
[f] Berlin, Germany
[g] TNO Healthy Living, Zeist, The Netherlands
[h] TNO Triskelion, Zeist, The Netherlands

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ABSTRACT

Identification of allergenic foods of public health importance should be based on well-defined criteria. Björkstén et al. (2008) proposed that the criteria should assess the evidence for an IgE mechanism, the reaction, the potency and the severity of the effect of the food and its prevalence. This study evaluated the application of the proposed criteria based on published reports. Publications were selected from two databases to test whether the descriptions for ranking the level of evidence for each criterion were unambiguous and covered the full range of levels of evidence regarding seven foods, five known to be allergenic and two negative controls. The options available to rank the quality of evidence were appropriate but needed refinement to improve clarity and conceptual value. The criteria were helpful to assess known IgE-dependent allergens, and to exclude the non-allergenic substances. The criteria framework discriminated between papers with high, moderate and low quality of evidence. The advantage of using the proposed criteria is to make the decision-making process and rationale explicit. The framework helps to identify gaps in knowledge and to uncover the level of heterogeneity of the evidence thus guiding research and providing a basis for sound risk management decisions.

1. Introduction

Food allergy is the result of a response of the immune system to normally harmless food components, usually proteins. Symptoms associated with food allergies vary greatly. Allergic symptoms occur most commonly in the mouth (swelling of the lips or tongue, mucosal itching), digestive tract (stomach cramps, vomiting, diarrhea), the skin (hives, rashes or eczema), and the airways (wheezing or breathing problems). Occasionally, severe systemic reactions such as anaphylaxis occur.

While food-allergic reactions appear to be linked to several mechanisms (Jyonouchi, 2008), the focus of regulatory measures is IgE-mediated food allergy because it causes the most severe (anaphylactic) reactions, and represents the best characterized and diagnosable form of food allergy.

A large number of foods have been reported to provoke allergic reactions in sensitive individuals (Hefle et al., 1996), but the number of allergenic foods with a significant impact on public health importance is much more limited. Prioritisation according to the public health impact is essential to ensure that scarce resources are allocated in such a way that they are most effective. Therefore it is imperative for regulators to decide whether a food allergen is of public health importance to such an extent that it needs to be actively managed. Classification of allergenic foods in terms of their importance to public health would benefit from clearly defined criteria. It would help to decide priorities and thus improve management of allergenic foods by focusing resources to where they are needed.

An Expert Group under the aegis of the ILSI Europe Food Allergy Task Force proposed a set of criteria to assess the strength of evidence of the available literature on a given allergen. The criteria

Abbreviations: DBPCFC, double blind placebo-controlled food challenge; IgE, immunoglobulin E; FARRP, Food Allergy Research and Resource Program; SPT, skin prick test.

* Corresponding author. Address: ILSI Europe, Avenue E. Mounier 83, Box 6, B-1200 Brussels, Belgium. Tel.: +32 2 771 00 14; fax +32 2 762 00 44.
E-mail address: publications@ilsieurope.be (J.H.M. van Bilsen).

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proposed by the Expert Group (Björkstén et al., 2008) focused on three groups of factors: clinical issues, population elements and modulating factors. The first group of factors (clinical issues) concerns confirmation that a food can cause an IgE-mediated adverse reaction. The different types of available clinical data and the weight they should be given are based on their quality regarding a) confirmation of sensitization (presence of specific IgE antibodies) and b) confirmation of a causal relationship between a clinical reaction and the ingestion of the suspected food. The observed clinical symptoms could provide information regarding the severity of the observed reactions and the potency of the allergen (in this paper i.e. the minimum doses of a food required to provoke adverse reactions in a sensitized individual). The second group of factors (population elements) permits quantitative conclusions to be drawn about the population at risk taking into account the prevalence of the food allergy and the exposure to the allergen. Finally, the last group of factors (modulating factors) further assesses the probability and extent of exposure to an allergenic food by focusing on the form of allergen in the food (hydrolyzed, denatured, native) and the impact of refining/processing of food on allergenicity.

Following these principles a framework was developed to appraise the strength of the available information to assess the public health importance of a food allergen (Björkstén et al., 2008). This framework facilitates the process of reaching agreement and makes clear the rationale for decisions by defining explicit criteria against which to evaluate the existing evidence. The advantage of this approach is that it makes the decision-making process explicit and, hopefully more consistent.

The present study tested and reviewed the application of the proposed criteria (Björkstén et al., 2008) to determine how readily this approach could be used in practice. As such (i) it offers guidance on how to interpret the literature in terms of strength of the evidence, (ii) it offers an objective method for identifying gaps in our knowledge and (iii) it can provide a basis for assessing the public health relevance of the allergenicity of a food item. Based on the review, refinements and some modifications to the criteria are proposed.

2. Materials and methods

2.1. Data sources

The main purpose of this project was to assess the suitability of each criterion as proposed by Björkstén et al. (2008) and not to assess the whole literature available to reach a conclusion about the food items examined. Therefore, a small number of papers were retrieved from those obtained in our literature search. The following foods or substances were used as illustrative examples: soybean, milk (including papers on lactose intolerance), peanuts, lupine, buckwheat and sulfites.

The selection of papers to evaluate published data on allergenic foods was obtained from two sources:

1) the Food Allergy Research and Resource Program (FARRP, University of Nebraska) database which specialises in allergenic foods and contained 16,688 articles published from 1910 up to December 2008 at the time of retrieval (peer-reviewed articles, abstracts, reports including government regulatory actions, scientific journals, food industry-focused journals, analytical methods papers, case reports and book chapters);
2) the US National Library of Medicine's Medline service to select papers that provided evidence for an IgE-mediated mechanism and/or the prevalence of allergy for the chosen food items not sufficiently covered by the FARRP database.

2.1.1. Selection of relevant articles

The FARRP database was searched between 16 October and 5 December 2008 using as keywords the food substances of interest (Table 1, column A) which were linked with keywords available in the FARRP database (Table 1, column B): death/fatal, processing, double blind placebo-controlled food challenge (DBPCFC), threshold, diagnosis, mechanism and severe. Articles that seemed to meet a specific criterion in combination with the food in question were selected to be studied in more detail.

Additional Medline searches were performed for aspects insufficiently covered in the papers selected from the FARRP database. These Medline database searches were performed between 25 October and 13 December 2008. The selection of articles supporting the IgE-mediated mechanism was performed by combining food substances from column A with keywords from column C, and prevalence of allergenic food by combining food substance from column A with keywords from column D (Table 1). Publications were selected for further study that contained prevalence or IgE-mediated mechanism data in combination with the food in question.

2.2. Testing the ability of the adapted criteria to discriminate between different qualities of evidence

The selection process using FARRP and Medline as described in the previous section resulted in a set of papers with the highest level of evidence. To test the evidence for each criterion in the range described by Björkstén et al. (2008) and to assess whether the criteria themselves were clear and unambiguous, articles on peanut allergy which differed in terms of the quality of the evidence were chosen for further assessment. Three members of the Expert Group and authors of this paper (GFH, RJR, RWRC) were invited to select a number of papers and the criteria for identifying the strength of evidence for allergenic foods of public health importance were applied to these papers independently by JHMB and the Expert Group members to establish the level of scientific evidence.

3. Results and discussion

3.1. IgE-mediated mechanism (Table 2)

During the review of the selected papers using the Björkstén criteria (Table 2A), the expert committee concluded that the description of the criteria, as they applied to the weight of evidence, required clarification since certain definitions were not specific enough to assign unambiguously a level of evidence. In the Björkstén criteria, the highest level of evidence (level 1) is described as 'At least two studies, in which the patient samples and food proteins are well defined, demonstrating the presence of bound IgE antibodies'. After evaluation, the definition 'well defined' in level

Table 1
Keywords used for selection of relevant articles from FARRP (columns A and B) and medline databases (columns A, C, D).

A Food substance	B All criteria	C IgE-mediated food allergy	D Prevalence
Buckwheat	Death/fatal	Allergy	Allergy
Lupine[a]	Processing	IgE	Food challenge
Milk	DBPCFC	DBPCFC	Epidemiological study
Peanut	Threshold	Clinical signs	Challenge
Soybean	Diagnosis		Intolerance
Sulfites[a]	Mechanism		Prevalence
Lactose	Severe		Cohort

[a] Both the UK and US-spelling of lupin (UK)/lupine (US) and sulphite (UK)/sulfite (US) were used upon entering the databases.

Table 2A
Type and level (weight) of evidence of clinical data according to criteria defined by Björkstén et al. (2008).

Data supporting	Type of evidence	Level of evidence
IgE-mediated mechanism	At least two studies, in which the patient samples and food proteins are well defined, demonstrating the presence of bound IgE antibodies	1
	Serological studies showing specific IgE binding to foods/extracts	2
	Studies of small numbers of serum samples from patients who are not adequately characterized	3
Adverse reactions caused by IgE-mediated reactions	Systematic DBPCFC[a,b] studies in well-characterized patients, with defined doses of specific food and with specific bound IgE antibodies	1
	Series of patients with well-documented reactions to suspected food, confirmed by DBPCFC[a], and with IgE antibodies	2a
	As above, but not confirmed by DBPCFC[a,b]	2b
	Case reports of clinical symptoms and the presence of food specific bound IgE antibodies, but not confirmed by DBPCFC	3
	Elimination diets leading to resolution of symptoms	4
Potency	Threshold studies with good range of doses and adequate numbers of well-characterized participants, preferably multi-centre	1
	Other threshold studies	2a
	Case reports describing reactions to low doses with well-documented evidence of dose	2b
	Case reports describing reactions to low doses with documented evidence of dose	3
Severity	Systematic threshold studies demonstrating thresholds for reactions of different severity (e.g. subjective vs mild objective)	1b
	Series of patients demonstrating reactions to different doses, preferably in same individuals	2
	Case reports demonstrating reactions to different doses	3
	Data from patient registers of severe reactions	3–4
	History of safe use	4
Prevalence	Epidemiological studies in defined populations, including verification of IgE antibodies and DBPCFC	1a
	As above but without DBPCFC	1b
	Epidemiological studies based on validated questionnaires	2
	Surveys of allergy clinic patients and other subgroups	3
	Registers of severe allergic reactions	3

[a] Double-blind placebo-controlled food challenge.
[b] And open challenges for infants.

1 was supplemented by adding the requirement that the details in the article should be sufficient to be reproducible by an independent researcher. To confirm sensitization, serologic tests that measure the presence of specific IgE to a particular allergen, are commonly used, as described in levels 1 and 2. However, in vivo skin prick testing (SPT) is equally valid and often preferred (Niederberger et al., 2001; Tresch et al., 2003). Therefore, SPT was added as evidence for sensitization (in both levels 1 and 2). Cellular basophil activation tests may provide complementary information in addition to skin tests and allergen-specific IgE determinations, but are not primary diagnostic measures (de Weck et al., 2008).

The last modification of the criteria supporting the IgE-mediated mechanism refers to the required number of studies containing data supporting an IgE-mediated mechanism to reach the lower levels of evidence (level 2 and 3). The Björkstén description of 'Serological studies' and 'Studies' were changed to 'At least 2 studies'.

Evaluating the selected articles using these modified criteria (Table 2B), resulted in the conclusion that the highest level of evidence (level 1) was met for an IgE-mediated mechanism for soybean, milk, lupine, buckwheat and peanut (references used: soybean (Ballmer-Weber et al., 2007; Mittag et al., 2004b); milk (Garcia-Ara et al., 2004; Saarinen et al., 2005; Skripak et al., 2008); lupine (Lindvik et al., 2008; Peeters et al., 2007b); buckwheat (Park et al., 2000; Choi et al., 2007); peanut (Flinterman et al., 2006; Peeters et al., 2007a; Wensing et al., 2002)). As expected, no publications were found to support an IgE-mediated mechanism for lactose or sulfites.

For emerging suspected allergenic foods, the first step in assessing available evidence is to establish whether any observed reactions are IgE-mediated. To confirm sensitization, serologic tests that measure the presence of specific IgE to a particular allergen, are commonly used. The revised criteria as described in this manuscript add SPT data as evidence to support an IgE-mediated mechanism. Both positive SPTs and presence of specific serum IgE demonstrate sensitization rather than allergy. However, SPTs have a high negative predictive value, and an individual with a negative SPT response is highly unlikely to have an immediate type I allergy to that food (Hill et al., 2004; Niggemann and Beyer, 2005; Rance et al., 2002). Furthermore, SPT can often be performed in circumstances where antibody measurements are impractical or difficult (e.g. highly labile allergens).

Once good evidence is available that suspected allergens do not act through an IgE-mediated mechanism, further assessment for that food item is not required in the present context.

3.2. Adverse reactions caused by IgE-mediated reactions

The DBPCFC is often described as the "gold standard" for confirmation of a causal relationship between a clinically observed reaction and the ingestion of a suspected food. A number of reviews have outlined this procedure, and efforts to standardize challenge materials are underway (Bock et al., 1988; Bindslev-Jensen, 2001; Bindslev-Jensen et al., 2004; Taylor et al., 2004; Flinterman et al., 2006). The selected articles showed great variability in terms of how thoroughly the clinical studies were described, particularly regarding the protocols used and the quality of reporting test materials, food matrices and patient characteristics. The criteria in Björkstén et al. (2008) were not adequate to distinguish these differences in levels of evidence.

In the Björkstén criteria (Table 2A), the highest level of evidence (level 1) is described as 'Systematic double-blind placebo-controlled food challenge (DBPCFC) studies in well-characterized patients, with defined doses of specific food and with specific bound IgE antibodies'. The definitions 'well characterized' (level 1), 'defined' (level 1) and 'well-documented' (level 2) were supplemented by adding the requirement that "the level of detail should be sufficient for the study to be reproducible". DBPCFC studies should include the description of the food matrix with an appropriate placebo-control. Furthermore, the SPT was again included as evidence to confirm sensitization (levels 1, 2 and 3). The final modification of the criteria supporting data that the adverse reactions were caused by IgE-mediated reactions refers to the description of the type of evidence for level 2: the original sub-levels of evidence were removed (level '2a' and '2b') as they were found

Table 2B
Type and level (weight) of evidence of clinical data according to modified criteria.

Data supporting	Type of evidence	Level of evidence
IgE-mediated mechanism	At least two studies, in which the patient samples and food proteins are well defined[a], demonstrating the presence of bound IgE antibodies and/or a positive SPT[e]	1
	At least 2 serological studies showing specific IgE binding to foods/extracts and/or a positive SPT	2
	At least two studies of small numbers of serum samples from patients who are not adequately characterized	3
Adverse reactions caused by IgE-mediated mechanisms	DBPCFC[c,d] studies in well-characterized[a] patients, with defined doses of specific food[a] in well described matrix [f] and with specific bound IgE antibodies and/or a positive SPT	1
	Series of patients with well-documented[a] history of reactions to suspected food, confirmed or not by DBPCFC[c], and with specific bound IgE antibodies and/or a positive SPT	2
	Case reports of clinical symptoms and the presence of food specific bound IgE antibodies and/or a positive SPT, but not confirmed by DBPCFC	3
	Elimination diets leading to resolution of symptoms	4
Potency	One or more threshold studies with good range of doses[b] and adequate numbers of participants with documented clinical symptoms of allergy, covering at least two centres. Two or more level 2 threshold studies could add up to level 1	1
	Other threshold studies	2
	Case reports describing reactions to quantitatively estimated low doses	2
	Case reports describing reactions to qualitatively estimated low doses	3
Severity	Objective signs confirmed by physician, preferably classified according to scientifically accepted classification system (e.g. according to Mueller, 1966)	1
	Subjective symptoms reported by patient in DBPCFC study for repeated doses	2
	Historical objective signs indicated by patient or subjective signs reported by patient in DPBCFC study for single dose	3
	Historical subjective symptoms indicated by patient	4
Prevalence	Epidemiological studies in general community population, including verification of sensitization by IgE antibodies or positive SPT, presence of clinical symptoms and DBPCFC[d]	1
	As above but without DBPCFC[d]	2
	Epidemiological studies based on questionnaires for clinical symptoms and sensitization in the general population	2
	Epidemiological studies based on questionnaires for clinical symptoms or sensitization in the general population	3
	Surveys based on general clinics patients (e.g. general practitioners, children clinics)	4
	Registers of severe allergic reactions	4

[a] Level of details sufficient to be reproducible.
[b] Dose-spacing should consist of doubling doses or involve a semi-logarithmic progression, starting at a dose low enough not to provoke a reaction in any participant. Moreover no effect and effect level of clinical signs should be included.
[c] Double-blind placebo-controlled food challenge.
[d] Or open challenges for infants.
[e] skin prick test, preferably performed according to the accepted guidelines.
[f] Matrix with appropriate placebo-control (with identical matrix composition as the matrix of active allergic material).

unhelpful for distinguishing between different qualities of evidence, both descriptions were considered appropriate for level 2 of evidence.

Assessing the selected publications using the adapted criteria (Table 2B), resulted in publications with the highest level of evidence (level 1) for IgE-mediated food-induced allergic reactions for soybean, milk and peanut (Table 3A). Some of the selected publications on lupine and buckwheat contained level 2 evidence since they were based on open oral challenges in children and/or DBPCFC (matrix, dosing, observed adverse reactions) but were poorly described (Lindvik et al., 2008). No publications on lactose or sulfites were found to support an IgE-mediated mechanism for the reactions induced by these substances.

Table 3A
Clinical data supporting level (weight) of evidence. (a). Allergenic food-induced adverse reactions caused by IgE-mediated reactions.

Allergen	Supporting evidence	Level of Evidence			
		1	2	3	4
Soybean	Ballmer-Weber et al. (2007)	X			
	Mittag et al. (2004b)	X			
Milk	Garcia-Ara et al. (2004)	X			
	Skripak et al. (2008)	X			
Lactose	No publications found				
Lupine	Lindvik et al. (2008)		X		
	Peeters et al. (2007b)	X			
Buckwheat	Park et al. (2000)	X			
	Choi et al. (2007)		X		
	Sohn et al. (2003)		X		
Peanut	Peeters et al. (2007a)	X			
	Wensing et al. (2002)	X			
Sulfites	No publications found.				

For emerging suspected allergens, the available data may only support an IgE-mediated reaction at low levels of evidence, as clinical reports may only include limited numbers of case studies. However, even if evidence for an IgE-mediated mechanism is of relatively low quality, the remainder of the framework can be applied to assess the public health importance of the food item in question as an allergenic food, while noting that better quality evidence is still required regarding the IgE-mediated mechanism. If the criterion for an IgE-mediated food allergy is not met further assessment is unnecessary.

3.3. Allergenic potency

The term allergenic potency can either be understood as the amount of an allergenic food required to sensitize an individual, or as the amount of food required to elicit a reaction in an already sensitized individual. In this paper and in Björkstén et al. (2008) the amounts of food needed to provoke adverse reactions are considered relevant since risk management of common allergens aims to reduce the probability of adverse reactions in allergic individuals, rather than preventing them from becoming allergic.

The highest level of evidence (level 1) is described by Björkstén et al. (2008) as 'Threshold studies with good range of doses and adequate numbers of well-characterized participants, preferably multi-centre'. In this study the term 'Threshold studies' were

specified to be 'One or more threshold studies'. The definition 'good range of doses' was specified by the requirement that dose-spacing should be doubling doses or a semi-logarithmic progression, starting at a dose low enough not to provoke a reaction in any participant (e.g. Taylor et al. 2004). In addition, the lack of an effect or the intensity of clinical signs should be included. The term "adequate numbers" was not analysed in detail, but experience with dose-distribution data which threshold studies generate would suggest that a minimum of 20 subjects would be sufficient in studies meeting the other criteria. The term 'well-characterized participants' was replaced by 'participants with well documented clinical symptoms of allergy', since such threshold studies are obviously conducted in well documented food-allergic patients. In the adjusted criteria, to reach level 1 of evidence, the threshold study should be carried out in at least two centres.

The definitions 'well-documented' (level 2b) and 'documented evidence of dose' (level 3) were refined by specifying quantitatively and qualitatively estimated low doses.

Moreover, the original sub-levels of level 2a and 2b of evidence were removed and both were considered level 2, as the distinction between them did not improve the assessment of the quality of evidence.

Most of the selected articles were classified as level 2 evidence, but in many instances there was more than one threshold study at level 2 of evidence, describing independent evidence and the final assessment was judged to constitute level 1 evidence. It should be noted that studies are not always specifically designed to determine a threshold but valuable data can arise from studies exploring low dose challenges (e.g. immunotherapy study (Leung et al., 2003; Nelson et al., 1997) and cross-reactivity studies (Mittag et al., 2004a; Peeters et al., 2007b)).

For all tested food substances, the highest level of evidence (level 1) for allergenic potency was reached based on the existence of at least 2 papers at level 2 (references used: soybean (Ballmer-Weber et al., 2007; Sicherer et al., 2000); milk (Garcia-Ara et al., 2004; Skripak et al., 2008); lupine (Peeters et al., 2007b; Shaw et al., 2008; Lindvik et al., 2008); buckwheat (Sohn et al., 2003; Park et al., 2000); peanut (Flinterman et al., 2006; Peeters et al., 2007a).

The assessment of potency is complicated by the large individual variations in the allergic response pattern to the same food and by the variability of the food itself. For instance, the amount of Mal d1 in apples is influenced by the method of cultivation, degree of maturity and storage conditions of the fruit (Asero et al., 2006; Botton et al., 2008; Vieths et al., 1994). Processing techniques may change allergenic properties of foods (Paschke, 2009; Sathe and Sharma, 2009).

3.4. Prevalence

The best available information to estimate the prevalence (number of allergic individuals in a population at a specific time) of a specific food allergy includes several critical features: (a) a study of the general population; (b) clinical demonstration of adverse reactions to the allergen preferably by DBPCFC; (c) and clinical documentation of an IgE-mediated mechanism for the adverse reaction. Without the DBPCFC, the prevalence may be an overestimate. As mentioned before, individuals can be sensitized (food-specific IgE) without clinical reactivity. Nonetheless, if DBPCFC data are lacking, but data that indicate the presence of food-specific IgE in combination with histories of (severe) clinical reactions to food are available, these combined data may provide a suitable estimate of prevalence.

Björkstén et al. (2008) assigned the highest level of evidence to an epidemiologic study in defined populations with confirmatory presence of allergen-specific IgE and with DBPCFC (level 1a), or without DBPCFC (level 1b). We believe that the original sub-levels within level 1 were unwarranted since prevalence data without DBPCFC confirmation are of a lower level of evidence than data with DBPCFC confirmation. Thus we modified the criteria levels from 1a and 1b to level 1 and level 2 respectively.

The Björkstén et al. level 2 of weight of evidence described 'epidemiological studies based on validated questionnaires'. Unfortunately, it is often not possible to check whether the questionnaires used in epidemiological studies are properly validated. Moreover, if such a questionnaire for clinical symptoms is accompanied by confirmation of sensitization, the weight of evidence is higher than when there is no confirmation of sensitization. Therefore the description of level 2 was adapted by eliminating the term 'validated' and the use of questionnaires without confirmation of sensitization were assigned level 3 of evidence. If only sensitization data are provided in the general population, this is also considered to be only level 3 of evidence. The Björkstén criteria describing level 3 ('surveys of allergy clinic patients and other subgroups' or 'registers of severe allergic reactions') were considered a lower level of evidence for prevalence than the newly introduced level 3, and changed into level 4 accordingly. The last modification of the criteria supporting prevalence refers to the group of patients that undergo surveys to obtain prevalence data. The Björkstén criteria describe surveys on allergy clinic patients and other subgroups. Although data from studies within an allergy clinic setting may be informative for assessing the relative contribution of each food allergen to the level of health care demand of a specialty, the patients accessing this service are unrepresentative of the general population to estimate prevalence of the population concerned. Therefore the revised criterion refers to surveys based on general clinics instead of specialized services.

Assessing the selected publications using the adapted criteria (Table 2B), resulted in a variety of levels of evidence, ranging from level 1 to level 4 (Table 3B). Relatively few reports have included DBPCFC in assessing the prevalence of food allergy (Zuberbier et al., 2004; Osterballe et al., 2005; Young et al., 1994; Jansen et al., 1994; Eggesbo et al., 2001; Vlieg-Boerstra et al., 2004; Roehr et al., 2004). A meta-analysis, conducted under the aegis of EuroPrevall, a large research study on food allergy funded by the European Commission, revealed considerable heterogeneity in study design and underlined the need for standardized methods (Rona et al., 2007). Many studies have been based on perception of food reactions using questionnaires. Self-administered questionnaire surveys are good for collecting data from all groups in a community and they are also less time-consuming for researchers as they do not have to meet people. However, there are problems with questionnaires such as people misinterpreting the questions and a low response rate which decrease the value of the study. Prevalence estimates based only on questionnaires usually exaggerate the frequency of food allergy (Rona et al., 2007).

Table 3B
Prevalence of food allergy.

Allergen	Supporting evidence	Level of Evidence			
		1	2	3	4
Soybean	Sicherer et al. (2000)				X
	Mittag et al. (2004b)				X
Milk	Saarinen et al. (1999)	X			
	Schrander et al. (1993)	X			
Lupine	Moneret-Vautrin et al. (1999)				X
	Shaw et al. (2008)				X
Buckwheat	Takahashi et al. (1998) (abstract consulted only) NB. Only one publication last 20 years			X	
Peanut	Hourihane et al. (2007)	X			
	Grundy et al. (2002)		X		

Some studies use subpopulations, instead of the general populations to screen for an allergy. Moneret-Vautrin estimated the prevalence of lupine allergy to be 27% in a series of 24 peanut-allergic individuals in France (Moneret-Vautrin et al., 1999). The prevalence of lupine allergy could be estimated from the prevalence of peanut allergy which is approx. 1.1% of the general population in the US (Sicherer et al., 1999). A limitation of the study is that it assumes that all lupine-allergic individuals are also peanut allergic. In addition, the 1.1% estimate of the prevalence of peanut provides low level evidence because it is based on a telephone survey.

3.5. Severity

Symptoms caused by food allergies can vary greatly according to severity, timing, organ involved and depend on the amount of food eaten. Furthermore a given amount of food may provoke a different reaction on different occasions. Symptoms usually appear within 10 min to two hours after eating the allergenic food. In the Björkstén criteria (Table 2A), the classification of weight of evidence of severity was based on the quality of the studies/reports in which severity was monitored. We believe that the classification should be based on the strength of evidence of the severity classification system of the clinical reactions. Therefore, in the adapted criteria, all levels of evidence for severity were revised (Table 2B). The starting point of the revision was that objective signs provide a higher level of evidence of severity than subjective symptoms. If subjective signs are observed for repeated doses, they are more convincing evidence of severity than if subjective signs are observed for a single dose. These starting points led to a classification of weight of evidence for severity in 4 levels, ranging from objective signs confirmed by a physician (highest level of evidence) to historical subjective symptoms indicated by the patient (lowest level of evidence).

Evaluating the selected articles using these adapted criteria resulted in the highest level of evidence (level 1) for severity of allergic reactions for all tested foods (references used: soybean (Ballmer-Weber et al., 2007; Sicherer et al., 2000); milk (Garcia-Ara et al., 2004; Calvani et al., 2007); lupine (Peeters et al., 2007b; Shaw et al., 2008; Lindvik et al., 2008); buckwheat (Sohn et al., 2003; Choi et al., 2007; Park et al., 2000); peanut (Flinterman et al., 2006; Peeters et al., 2007a).

Ideally, the challenges are conducted in a DBPCFC-study in a hospital setting with careful monitoring of the patients and where full emergency resources are available. The challenge is discontinued when objective symptoms occur, or when convincing subjective symptoms occur for at least three times or last for more than 45 min (Flinterman et al., 2006; Peeters et al., 2007a). However, allergic symptoms often occur inadvertently in poorly monitored environments outside a hospital and may resolve spontaneously or with treatment prior to hospital arrival. Classification systems of allergic reactions need to be relatively simple and easy to interpret and apply retrospectively. Grading systems have been designed (Brown, 2004; Mueller, 1966) for the classification of allergic reactions that have been adapted and used for the classification of food allergic symptoms by others (Peeters et al., 2007b).

3.6. Testing discriminatory power of quality of evidence descriptions (Table 4)

The FARRP and MEDLINE search strategy described in the materials and methods sections resulted in a selection of articles with the highest level of evidence. To test whether the scientific criteria were able to discriminate papers with high/moderate/low quality of evidence and whether the criteria were clear and unambiguously described, articles on peanut allergy were selected for further assessment of the criteria.

Articles selected to test the weight of evidence of prevalence were ranked identically by JHMB and RJR. Articles on IgE-mediated mechanism and adverse reactions caused by IgE-mediated reactions were also ranked identically by JHMB and GFH, demonstrating that the criteria were described in sufficient detail. However, during evaluation of the level 1 description of adverse reactions, the term 'systematic' (i.e. patients specifically recruited for the study) was eliminated because, in most papers, it cannot be checked whether patients were specifically recruited for a DBPCFC study.

Assessing the selected articles to test the potency criteria led to two discrepancies between JHMB and RWRC which were related to the required amount of individual details provided in an article to reach the highest level of evidence: Leung (Leung et al., 2003) describes an immunotherapy study in which threshold doses were established by DBPCFC to evaluate the effect of the immunotherapy. The study was conducted at seven centres in the United States in which 81 patients completed the study. However, the description of the patients was poor since details on individuals were not provided. The paper by (Taylor et al., 2002) describes a round table conference in which threshold data from different centres using different protocols were shared, but data on individuals were not provided. Despite the initial discrepancies, a short discussion led to the agreement of ranking so both studies were classified as level 2 of evidence.

Assessing the selected articles to test the severity criteria led to two initial discrepancies between JHMB and RWRC which were related to the description of the number of doses (Nelson et al., 1997) given in a DBPCFC and the absence of challenge data (Vander Leek et al., 2000). Despite the discrepancies, a short discussion led to the agreement of ranking, which indicates the lucidness of the defined criteria.

The above described exercise led to further refinement of the criteria by the Expert Group members and JHMB. The exercise showed that the modified scientific criteria are able to discriminate papers with high and moderate/low quality of evidence. Despite some initial differences in ranking on potency and severity, the differences were generally small and resolved through discussion.

3.7. Future challenges

Once sufficient evidence is available that a reaction to a food is IgE-mediated, it is appropriate to address other criteria: potency of the allergen, severity of the reactions, its prevalence and exposure. For newly introduced foods, the criteria will initially only provide low levels of evidence based on case reports of clinical symptoms, possibly followed by potency and severity reports and finally prevalence information.

In the ideal situation, all available data would conform to level 1 evidence and the papers agree closely. In practice, papers are not written for the purpose of complying with the criteria that we are developing and the results between studies are heterogeneous.

The framework addressed the evaluation of the quality of the data on the public health relevance of allergens, but did not provide an actual evaluation of the public health relevance of an allergen. For example it may be difficult to directly compare the public health impact of foods causing relatively mild reactions but very common in the population to the impact of foods causing very severe reactions in a few individuals.

A risk scoring system should be developed in which all available levels of evidence for each criterion (e.g. prevalence of peanut allergy: level 1 of evidence) should be collected, in combination with the actual data of the criteria (e.g. prevalence of peanut allergy 1.1%). Eventually risk scores should be attributed to the combined available information for each newly introduced food. Such an overall scoring system has not been developed yet but is very useful for proper risk assessment. One could think of several

Table 4
Testing discriminatory power of quality of evidence descriptions.

Literature reference	Ranking by JHMB (A), Expert Group member (E) and agreement of ranking (X)			
	Level of evidence			
IgE-mediated mechanisms	1	2	3	4
Peeters et al. (2004)			AEX	
Mittag et al. (2004a)	AEX			
Wensing et al. (2003)	AEX			
Wensing et al. (2002)	AEX			
Peeters et al. (2007b)	AEX			
Adverse reactions caused by IgE-mediated reactions				
Peeters et al. (2004) (no clinical data)	–	–	–	–
Mittag et al. (2004a) (specifically recruited? → adaptation criteria)	AEX			
Wensing et al. (2003) (three patients)			AEX	
Wensing et al. (2002)	AEX			
Peeters et al. (2007b) (specifically recruited? → adaptation criteria)	AEX			
Potency				
Morisset et al. (2003)		AEX		
Leung et al. (2003)	A	EX		
Wensing et al. (2002)		AEX		
Taylor et al. (2002) (no individual data; multiple centres and protocols)	A	X	E	
Nelson et al. (1997)		AEX		
Severity				
Le et al. (2008) (data based on questionnaire)			AEX	
Kagan et al. (2003a) (no challenge data shown for objective/subjective interpretation)			AEX	
Vander Leek et al. (2000) (no challenge data shown)	E		AX	
Sicherer et al. (2000)	AEX			
Rance and Dutau (1997)	AEX			
Nelson et al. (1997) (challenge stopped if moderately severe abdominal pain)		A	EX	
Prevalence				
Sicherer et al. (1999) (questionnaire)			AEX	
Emmett et al. (1999) (interviews)			AEX	
Pereira et al. (2005)	AEX			
Kagan et al. (2003b)	AEX			
Osterballe et al. (2005)	AEX			
Roehr et al. (2004)	AEX			
Marklund et al. (2004) (questionnaire)			AEX	
Altman and Chiaramonte (1996) (questionnaire)			AEX	
Roberts et al. (2005) (SPT only)			AEX	
Bjornsson et al. (1996) (questionnaire + IgE)		AEX		

appropriate overall risk scoring systems e.g.: (i) a numerical scoring system, resulting in an aggregate numerical score; (ii) a two-dimensional parameter scoring system in which different parameters are mapped one against the other, ultimately resulting in a ranking into three categories: 'minor allergenic food', 'waiting room' (likely allergenic food requiring more research), or 'major allergenic food requiring risk assessment'; (iii) a scoring system in which the food in question is labelled as a major allergenic food, a minor allergenic food, potential major allergenic food (high priority research) or is likely to be a minor allergenic food (low priority research). The future work of the ILSI Europe Expert Group will be to apply and incorporate this tool, designed to evaluate the quality of scientific evidence, into an overall weighed approach of establishing the actual public health importance of a given allergen.

4. Conclusion

This study evaluated the usefulness of the framework for the evaluation of the strength of evidence for allergenic foods proposed by Björkstén et al. (2008). The value of the criteria was tested on a selection of publications related to food allergy. One consequence of the assessment and the discussion in the Expert Group was a decision to modify some of the original criteria. Nonetheless we showed the usefulness of the Björkstén paper

- in offering guidance on how to interpret literature data in terms of strength of evidence, against the background of the spectrum of available levels of strength of evidence.
- in offering guidance for further targeted research to fill gaps in scientific knowledge.
- in serving as a basis for informing public health relevance and more broadly food safety risks.

The adapted framework was helpful to classify the literature for known IgE-dependent allergenic foods, and to exclude the negative controls (sulfite and lactose). The framework was able to discriminate papers containing high and moderate/low quality of evidence, thereby indicating the clarity and robustness of the framework. The criteria developed need users with adequate level of knowledge, but the advantage is that these criteria make the decision-making process explicit. The framework might be useful to identify gaps in knowledge of the emerging allergens (food properties, population factors, and exposure factors) or conflict in the evidence which can guide research priorities and guide proper risk management decisions. The evaluated framework has the potential to make a valuable contribution to the risk management of allergenic foods of public health importance. The framework addresses the evaluation of the quality of the data, but does not provide an actual evaluation of the public health relevance of an allergen. Guidance for the latter is subject of future developments.

Conflict of interest

No conflict of interest was declared.

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For further information about ILSI Europe, please email info@ilsieurope.be or call +32 2 771 00 14. The opinions expressed herein and the conclusions of this publication are those of the authors and do not necessarily represent the views of ILSI Europe nor those of its member companies.

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Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals

Steve L. Taylor [a,*], D.A. Moneret-Vautrin [b], Rene W.R. Crevel [c], David Sheffield [d], Martine Morisset [b], P. Dumont [b], Benjamin C. Remington [a], Joseph L. Baumert [a]

[a] Food Allergy Research and Resource Program, Department of Food Science and Technology, University of Nebraska-Lincoln, Lincoln, NE, USA
[b] Department of Internal Medicine, Clinical Immunology and Allergology, University Hospital, Nancy, France
[c] Safety and Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedford MK44 1LQ, United Kingdom
[d] Statistics Group, Unilever, Colworth Science Park, Sharnbrook, Bedford MK44 1LQ, United Kingdom

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ABSTRACT

Clinical records of 286 consecutive patients reacting positively with objective symptoms to double-blind, placebo-controlled oral peanut challenges at University Hospital, Nancy, France were examined for individual No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs). After fitting to a log-normal probability distribution model, the ED_{10} and ED_{05} were 14.4 and 7.3 mg (expressed as whole peanut), respectively, with 95% lower confidence intervals of 10.7 and 5.2 mg, respectively. Compared to results from a previous study where the ED_{10} was based upon individual peanut thresholds gleaned from 12 publications, a statistically significant difference was observed between the ED_{50}'s, but not the ED_{10}'s of the two probability distribution curves. The Nancy patient group contains more sensitive subjects than the group from the published literature thus contributing to the observed differences. Minimum eliciting dose-distributions for patients with histories of more severe reactions (grade 4 or 5; 40 subjects) did not differ significantly from those of patients with histories of less severe reactions (grades 1–3; 123 subjects). These data and this modeling approach could be used to establish population thresholds for peanut-allergic consumers and thereby provide a sound basis for allergen control measures in the food industry.

1. Introduction

Allergic reactions to peanut are among the most prevalent and severe of all food allergies (Hourihane et al., 2007; Bock et al., 2007; Yunginger et al., 1988). The inadvertent ingestion of peanut by peanut-allergic individuals is the leading cause of fatal food-allergic reactions (Bock et al., 2007; Yunginger et al., 1988). It has also been reported that exposure to trace amounts of peanuts can provoke allergic reactions in some peanut-allergic individuals (Taylor et al., 2002). Thus, careful and complete avoidance of peanuts has been advised for peanut-allergic individuals (Taylor et al., 1986). Peanut-allergic consumers face increasingly restricted food choices in complying with this advice due, in part, to the proliferation of advisory labels such as 'may contain peanuts' (Hefle et al., 2007).

Experience with clinical oral challenge trials indicates that exposures do exist below which individuals with confirmed peanut allergy will not experience allergic reactions (Taylor et al., 2002). An individual's elicitation threshold lies between the No Observed Adverse Effect Level (NOAEL), the highest dose that will not produce any adverse effect in that person and the Lowest Observed Adverse Effect Level (LOAEL), the lowest dose that produces an adverse effect (Taylor et al., 2009). The range of LOAEL doses for peanut-allergic individuals in clinical challenge trials spans 4–5 orders of magnitude – 0.5 mg up to 8000–10,000 mg of whole peanut (Taylor et al., 2009). The population threshold is defined as the largest amount of peanut that would not cause an adverse reaction in any individual within the total population of peanut-allergic individuals. But, of course, it is impossible to perform challenge tests on the entire peanut-allergic population, so population threshold estimates must be obtained from clinical food challenge trials conducted on defined groups of peanut-allergic individuals. The accuracy of those population threshold estimates will depend upon the representativeness of the selected population and the statistical approach used to model the distribution of the individual threshold doses from the clinical studies.

The US Food and Drug Administration has indicated that statistically-based risk assessment (including statistical techniques such as dose-distribution modeling) provides the ideal approach to the establishment of a population threshold for allergenic foods including peanut (Threshold Working Group, 2008). Taylor et al.

* Corresponding author. Tel.: +1 402 472 2833; fax: +1 402 472 5307.
E-mail address: staylor2@unl.edu (S.L. Taylor).

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(2009) used dose-distribution modeling to estimate the population threshold from individual threshold information for 185 peanut-allergic subjects obtained from 12 published clinical studies. From the NOAELs and LOAELs of these patients, a dose-distribution model was constructed using interval-censoring survival analysis (Taylor et al., 2009). An ED_{10} (the dose predicted to provoke a reaction 10% of the peanut-allergic population) of 8.4 mg of whole peanut was derived based on fitting the data to a log-normal distribution. In that study, the choice of the probability distribution model had little effect on the ED_{10} estimate. While that dataset was the largest on individual peanut thresholds assembled to date, the sufficiency of these data to establish a population threshold as a basis for risk management could be questioned. First, these data were obtained from 12 different published studies using various clinical challenge protocols. In particular, the use of different challenge doses in the various protocols created a large number of NOAEL/LOAEL intervals. Furthermore, the LOAEL dose could not be defined in 67/185 subjects which increases the uncertainty about the "true" population threshold dose (Taylor et al., 2009). Secondly, patient selection biases likely existed in these published studies since there was no evidence to suggest that the peanut-allergic subjects had been randomly selected. Furthermore, the NOAEL/LOAEL intervals could only be discerned for a fraction of the total number of peanut-allergic subjects included in these published studies which likely introduces additional bias (Taylor et al., 2009). However, there is strength in that analysis because the data come from a combination of 12 studies.

This risk assessment effort (Taylor et al., 2009) demonstrated that sufficient data exist for peanut to establish an estimate of a population threshold that could be used for regulatory and food industry action/management levels. However, because of the uncertainties noted above, a similar analysis based on data obtained from group(s) of peanut-allergic subjects where a consistent challenge protocol was used and where the patient population could be adequately characterized and selection biases could be minimized, or at least better understood would be important in establishing a better estimate of the population threshold. We describe the analysis of a large clinical dataset from University Hospital, Nancy, France where diagnostic peanut challenges had been conducted on all prospective peanut-allergic patients at that clinic using a consistent challenge protocol over a period of more than 10 years.

2. Patients

Patients (286, 162 males, <1–48 years of age (median 7.0 years)) were selected for diagnostic oral, double-blind, placebo-controlled peanut challenges (DBPCFC) at University Hospital, Nancy, France based upon either a history of possible previous allergic reactions to peanut, including anaphylactic shock, or sensitization to peanuts detected at an early age but no history of actual allergic reactions to peanuts as a result of being placed on a systematic avoidance diet. Apart from being peanut-allergic, they were unselected, consecutive patients who attended the clinic as part of the treatment of their allergy. Consecutive patients include all of the patients that self-selected to seek medical diagnosis of their peanut allergy at the Nancy France clinic and were enrolled in a low-dose food challenge (patients were not randomly selected for challenge). Although a proportion of patients received more than one peanut challenge over time, the data used here are from only the initial diagnostic challenge procedure.

3. Methods

DBPCFCs were conducted in a manner consistent with the consensus clinical protocol for threshold studies (Taylor et al., 2004). Anti-histamine treatment was stopped 7 days before challenge and inhaled corticosteroids and beta agonists were stopped 24 h before challenge. Patients were not challenged while, or within a week of suffering respiratory infections or rhinopharyngitis. DBPCFC was conducted on each subject using various doses of crushed roasted peanut in apple sauce (Moneret-Vautrin et al., 1995). An interval of 15 min was used between increasing doses of peanut. In general, one or two of three series of dosage progressions were used depending upon the described severity of historical reactions to peanut and the age of the patient (Table 1). Thus some patients started with Progression 1 while others started with Progression 2 depending on the physician's judgment about their potential reactivity. Occasionally, modifications of the progression were used instead. Both subjective and objective symptoms were recorded and generally, challenges were continued until objective symptoms were encountered or until the highest dose (7110 mg cumulative dose) had been consumed. Objective symptoms included any symptom that would have been discernable to clinical observers e.g. vomiting, urticaria, rash, angioedema, etc. Abdominal pain was considered an objective reaction only in children who did not experience symptoms in the placebo arm of the DBPCFC. Additionally, the abdominal pain should have lasted for more than 30 min or should have been of sufficient intensity to require treatment (glucocorticoid and H1 anti-histamine) to be considered an objective endpoint symptom. Crying; prostration; mood changes (grumbling child); pharyngeal, oral, or laryngeal pruritis; nausea; or palor were minor criteria that were used to support the abdominal pain symptom. Abdominal pain as the sole symptom was not considered an objective endpoint symptom in adult subjects. Adult subjects continued with the challenge until objective symptoms were experienced.

Occasionally, the next higher dose was administered at the physician's discretion in situations where the initial reaction was very mild and transitory. Individual NOAELs and LOAELs were recorded for each peanut-allergic patient based upon the cumulative dose eliciting the initial objective reaction. In the instances where very mild and transitory reactions were observed and the next higher dose was administered, the LOAEL was considered the cumulative dose where lasting objective reactions occurred and the NOAEL was considered the previous cumulative dose. If no adverse reaction was encountered at the highest dose in Progression 3, then the patient was not considered as peanut-allergic and was not included in the dataset.

The records of peanut-allergic patients were also screened for evidence concerning the history of severity of allergic reactions occurring to peanut before DBPCFC. Patients were identified as having a previous severe reaction if they gave a history of a Severity Grade 4 or 5 reaction (objective reactions occurring in three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension) (Astier et al., 2006). Other patients were identified as having a previous non-severe reaction if they gave a history of a Severity Grade 1–3 reaction (objective symptoms occurring in 1–2 organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, angioedema but not laryngeal edema, and/or asthma not requiring treatment).

Individual NOAELs and LOAELs for all peanut-allergic patients challenged over a 17-year period from 1991 to 2008 were analyzed by an Interval-Censoring Survival Analysis (ICSA) approach as previously described (Collett, 1993; Taylor et al., 2009). Data analyses and modeling were performed in SAS v9.1 (SAS Research Institute) using the procedure LIFEREG as previously described (Taylor et al., 2009). A log-normal dose-distribution model was used to estimate the ED_{10} and the ED_{05}, the doses predicted to provoke reactions in 10% and 5%, respectively, of the peanut-allergic population.

4. Results

4.1. Dose-distributions

Individual NOAELs and LOAELs based on objective symptoms for whole peanut were obtained for 286 patients over the 17-year time period. The ED_{10} and ED_{05} were 14.4 and 7.3 mg (expressed as whole peanut), respectively, with 95% lower confidence intervals of 10.7 and 5.2 mg, respectively (Table 2). Fig. 1 shows that differences were observed between the slope of the curve of the log-normal distribution model for this dataset and the distribution modeled separately from the evaluation of the individual thresholds of peanut-allergic subjects gleaned from the published clinical literature (Taylor et al., 2009). This difference is also reflected in the ED_{50} values (the dose predicted to provoke reactions in 50% of the peanut-allergic population) which were 1036 mg of whole peanut for publications dataset and 157 mg of whole peanut for the Nancy patient dataset. Since the 185 peanut-allergic subjects included in the original analysis of the individual thresholds of peanut-allergic subjects from the published literature included 21 subjects reported by the clinical group in Nancy, France (Taylor et al., 2009), those data points were removed before the dose-distribution modeling shown in Fig. 1 – an analysis of the remaining

Table 1
DBPCFC dose progression series.

Progression 1		Progression 2		Progression 3	
Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose
0.1	0.1	5.0	5.0	10.0	10.0
0.3	0.4	10.0	15.0	100.0	110.0
1.0	1.4	50.0	65.0	500.0	610.0
3.0	4.4	150.0	215.0	1500.0	2110.0
10.0	14.4	285.0	500.0	5000.0	7110.0
30.0	44.4	465.0	965.0		

All values reported in milligram whole peanut.

Table 2
ED_{10} and ED_{05} doses for whole peanut as assessed by the log-normal probability distribution models.

Source	Total no. of peanut-allergic individuals	ED_{10}	95% CI	ED_{05}	95% CI
Nancy data	286	14.4	10.7, 19.6	7.3	5.2, 10.4
Published papers[a]	164	14.1	6.6, 29.9	4.2	1.7, 10.1
Combined	450	12.3	9.0, 16.8	5.2	3.6, 7.4

All values reported in mg of whole peanut.
[a] Nine published studies yielded NOAELs and LOAELs for 164 peanut-allergic individuals. Twenty-one individuals from three papers (A, B, and D; see Taylor et al., 2009) were excluded from analysis to avoid potential duplication of individuals as these studies included individuals from the Nancy clinic.

164 subjects. The ED_{10} and ED_{05} of these two datasets and the combined dataset of 450 peanut-allergic subjects are presented in Table 2. The removal of the 21 Nancy patients from the original dataset caused the ED_{10} to increase from 8.4 to 14.1 mg because many of these subjects were among the most sensitive in that dataset. Four of these 21 subjects were left-censored individuals that reacted upon ingestion of the first dose (5 mg of whole peanut) in the challenge. The left-censored subjects have a profound effect in lowering the overall population threshold and, by taking these individuals out of the publications dataset, the overall ED_{10} estimate increased. This clearly shows the importance of designing low-dose challenge studies so that all individuals are interval-censored (have established NOAEL and LOAEL values). The ED_{10} and ED_{05} from this Nancy dataset are slightly higher than the estimates obtained from the evaluation of individual thresholds gleaned from the published literature (Table 2). From the combined dataset of 450 peanut-allergic subjects, the ED_{10} and ED_{05} were 12.3 and 5.2 mg (expressed as whole peanut), respectively, with 95% lower confidence intervals for the ED_{10} and ED_{05} of 9.0 and 3.6 mg, respectively (Table 2). The slight decrease in the ED_{10} and ED_{05} values in the combined dataset compared to the Nancy dataset can be attributed to the inclusion of three very sensitive interval-censored subjects (LOAEL values ranging from 0.5 to 1.6 mg) and five left-censored individuals from the publications dataset (164 total subjects) that, when analyzed with the more sensitive subjects in the Nancy dataset, further decreases the ED_{10} and ED_{05} values for the combined dataset. The estimates from the combined dataset and the Nancy dataset, however, are not significantly different.

4.2. Responses to challenge

Many of the subjects experienced multiple symptoms during the oral challenge. All of these symptoms are summarized in Table 3, both overall and according to dose progression, to which they had been allocated according to the physician's initial view of likely reactivity. Thus individuals who were thought likely to react at very low doses were started at 0.1 mg and challenged up to 44.4 mg. This ensured that an individual NOAEL was obtained for all but eight subjects. Almost all symptoms observed during challenges in all groups were mild. Adult subjects who experienced abdominal pain as their only initial symptom were continued in the oral challenge until objective symptoms were observed. In all cases, more severe

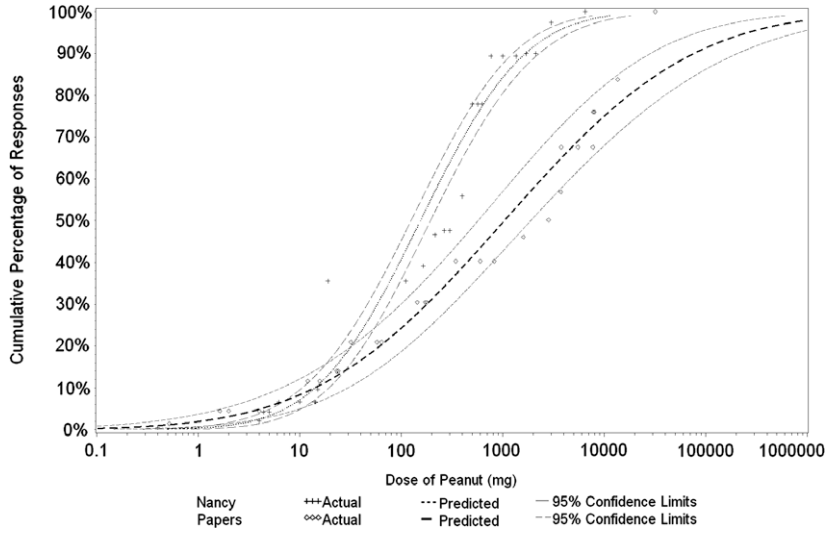

Fig. 1. Log-normal probability distribution models of individual peanut thresholds (expressed as whole peanut) for peanut-allergic individuals gleaned from publications and compiled from diagnostic challenge trials in Nancy, France.

Table 3
Summary of symptoms* reported on challenge for 286 peanut-allergic individuals.

Symptoms	Progression 1		Progression 2		Progression 3		Total	
	Number of reactions	%	Number of reactions	%	Number of reactions	%	Number of reactions	%
Conjunctivitis	3	5	27	14	5	14	35	12
Rhinitis	2	3	29	15	5	14	36	13
Hives	5	9	34	18	18	50	57	20
Angioedema	3	5	13	7	5	14	21	7
Rash or eczema	2	3	14	7	7	19	23	8
Sibilant rales (wheeze)[a]	2	3	24	13	6	17	32	11
Decrease PEF (20%)	0	0	22	11	4	11	26	9
Asthma	2	3	27	14	4	11	33	12
Tachycardia	0	0	11	6	5	14	16	6
Fall of BP	0	0	4	2	1	3	5	2
Vomiting	6	10	57	30	4	11	67	23
Abdominal pain (+ other symptoms)	30	52	117	61	17	47	164	57
Abdominal pain only	17	29	32	17	4	11	53	19
Diarrhea	4	7	12	6	2	6	18	6
Other objective symptoms	3	5	34	18	7	19	44	15
Subjective symptoms	15	26	66	34	10	28	91	32
Total number of peanut-allergic individuals	58		192		36		286	
Males	37		106		19		162	
Females	21		86		17		124	
Age (years) (median; range)	7.5	2.9–25	7.0	<1–48	5.5	1.4–22	7.0	<1–48

* Many subjects experienced multiple symptoms during the double-blind, placebo-controlled food challenge (DBPCFC). All symptoms were recorded according to the dose progression where the reactions occurred and total number of reactions for each symptom is provided.
[a] Sibilant rales (wheeze) are heard by auscultation and are the first sign of asthma crisis. Asthma was used only to describe when a subject was dyspnoeic.

objective symptoms such as vomiting or diarrhea occurred upon ingestion of increasing doses. A similar observation was also made by Ballmer-Weber et al. (2007) where 5 soy-allergic subjects with initial abdominal pain reacted with objective symptoms upon increasing the dose. More severe symptoms, such as a fall in blood pressure, were only observed occasionally, while they were never observed during Progression 1 (low dose). Interestingly, the symptoms experienced by those who reacted to the first (low dose) progression showed, if anything, somewhat milder symptoms than the other two groups. The most common symptoms were linked to the gastrointestinal tract, namely abdominal pain (includes those experiencing abdominal pain only and abdominal pain plus other symptoms) and vomiting, which were experienced by approximately 76% and 23% of patients, respectively.

4.3. Severity by history vs. reactive dose

Among the 286 peanut-allergic patients from Nancy, 163 subjects had experienced a reaction prior to challenge and information was available on the severity of those reactions. A total of 40 subjects were identified who had previously experienced severe reactions (Severity Grade 4 or 5) before the DBPCFC compared to 123 subjects who had experienced less severe reactions (Severity Grade 1–3). The threshold distribution of patients with histories of more severe reactions did not differ significantly from the threshold distributions from patients with histories of less severe reactions (data not shown). The ED_{10}'s for the two groups were quite similar (Table 4). In contrast, the ED_{10} for the remaining 123 patients, most of who did not present initially with a history of an allergic reaction to peanut was somewhat higher, although this difference was not statistically significant (Table 4). Previous oral exposure to peanut is uncertain in this group.

5. Discussion

Thresholds are needed to assess the risk posed by residues of allergenic foods particularly at the population level and to determine appropriate risk management strategies. Population thresholds are critical to the assessment of public health risk, the development of appropriate risk management approaches, and the establishment of regulatory safeguards for allergic consumers. Dose-distribution probability modeling has been identified as a promising approach to estimate population thresholds (Bindslev-Jensen et al., 2002; Crevel et al., 2007). While the US Food and Drug Administration indicated that such modeling would provide the ideal approach to the establishment of population thresholds for allergenic foods including peanut (Threshold Working Group, 2008), they have questioned whether enough data exist for such modeling. Recently, we demonstrated that sufficient data could be gleaned from the published literature for peanut to estimate doses predicted to elicit (mild) reactions (Perry et al., 2004) in 10% of the at-risk population with reasonable precision (Taylor et al., 2009).

We have now confirmed and strengthened our initial estimate of the population threshold for peanut. Individual NOAELs and LOAELs were found, respectively, for 278 and 286 peanut-allergic subjects by screening the records of University Hospital,

Table 4
ED_{10} doses* for whole peanut as assessed by the log-normal probability distribution model for Severity Grade.

Severity grade	Total no. of peanut-allergic individuals	ED_{10}	95% CI
Severe[a]	40	10.4	4.8, 22.6
Non-severe[b]	123	10.2	6.4, 16.1
No prior history[c]	123	27.0	17.4, 42.0

* All values reported in mg whole peanut.
Statistically valid ED_{05} estimates could not be provided due to the limited number of subjects in all of the severity grade classes.
[a] Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.
[b] Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%).
[c] History of prior allergic reactions and severity of reactions were not available. These individuals were identified as being sensitized to peanut by means of diagnostic tests.

Nancy, France. The ED_{10} (14.4 mg of whole peanut) obtained from this dataset is in reasonable agreement with the earlier estimate (8.4 mg) by the log-normal distribution model. When the 21 subjects from the Nancy clinic were removed from the earlier dataset to avoid possible duplications, the ED_{10} increased to 14.1 mg. These 21 subjects were among the most sensitive and included four left-censored subjects in the earlier dataset accounting for the difference. Some patient selection bias is obvious because the NOAELs and LOAELs of only the 10 most sensitive of 103 peanut-allergic patients could be discerned from one of those earlier Nancy publications (Morisset et al., 2003; Taylor et al., 2009). Furthermore, combining the two datasets allowed the estimation of the ED_{10} and the ED_{05} based on the NOAELs and LOAELs of 450 peanut-allergic subjects with a higher level of confidence. While the ED_{10}'s for the two datasets are quite similar, the dose-distribution curves are strikingly different as reflected in Fig. 1 and by the ED_{50}'s. The difference indicates that the Nancy dataset is weighted toward more sensitive peanut-allergic subjects.

The data on NOAELs and LOAELs from the Nancy patients offer some distinct advantages in comparison to the use of the information from the published literature. Population thresholds should ideally be based upon clinical data obtained from a representative sample of the entire peanut-allergic population. The published studies examined for our earlier population threshold estimate (Taylor et al., 2009) involved selected patients and were highly heterogeneous. NOAELs and LOAELs could only be identified or discerned for a proportion of the total number of subjects from some publications considered in the earlier study (Taylor et al., 2009). In contrast, the Nancy subjects were 286 consecutive patients with positive peanut challenges. The patient selection bias is thus reduced although the subjects do self-select to seek the medical diagnosis of their peanut allergy. Furthermore, the Nancy challenge protocol with three dosing progressions enhances the likelihood that the dosage range will encompass both the NOAEL and LOAEL. In fact, no right-censored subjects (LOAEL > highest challenge dose) were encountered in the Nancy group (such subjects would have been considered not to be peanut-allergic), while 67 such individuals were included among the 185 subjects in the earlier analysis (Taylor et al., 2009). The number of left-censored subjects (LOAEL = lowest challenge dose) was similar in the Nancy group (eight left-censored subjects) and the published studies group (nine left-censored individuals) (Taylor et al., 2009). Subsequently, we have re-analyzed the dose-distributions from the publications dataset with and without inclusion of the right-censored subjects (Table 5). The ED_{10} is slightly lower for the distribution without any right-censored subjects (6.1 mg of whole peanut) by comparison to the group that contains the 67 right-censored subjects (14.1 mg of whole peanut). Typically, clinical challenge trials are limited to several hours, leading to practical limitations in designing experiments that would ensure the identification of both NOAELs and LOAELs for all subjects. Thus, the use of the three dosage progressions in the Nancy clinic allowed determination of the individual NOAELs and LOAELs for all peanut-allergic subjects.

Another uncertainty regarding the development of population thresholds for peanut is the possible exclusion of patients with histories of severe reactions from clinical challenge trials (Taylor et al., 2002). Without studies on patients with histories of severe reactions, the possibility exists of a more sensitive sub-population, which might remain unprotected if risk management was based on the response of the less sensitive majority. In the previous estimate of the population threshold for peanut (Taylor et al., 2009), the selection of patients and the severity of the symptoms involved in their previous reactions was impossible to determine. However, in the Nancy group, patients with previous histories of severe reactions, including anaphylactic shock, were not excluded from the diagnostic challenges. Of 163 challenged patients with known previous histories of allergic reactions to peanut, 40 subjects had histories of severe reactions. But, as shown in Table 4, the ED_{10} for the severe reactors was essentially the same as that of the non-severe reactors. Thus, subjects with histories of severe allergic reactions to peanuts do not appear to represent a distinct sub-population with greater sensitivity. Interestingly, the ED_{10} for the remaining 123 subjects, most of whom had no history of previous reactions to peanuts, was higher. However, the eliciting doses for this group were still sufficiently low to indicate that they would be at risk from the ingestion of peanut. When setting action levels for regulatory purposes, the key criterion is safety. While it is impossible to be sure of protecting every single allergic individual against a reaction, it is important to demonstrate that, in the event of inadvertent exposure, any reaction will be mild. The data on the most sensitive individuals, namely those who reacted to the lowest amounts of peanut offer considerable reassurance in this respect, since all of them showed mild symptoms at the doses which elicited reactions (Table 3).

Using the combined dataset of 450 peanut-allergic individuals allows prediction of the ED_{10} and ED_{05} with a high level of confidence. In our opinion, these data should be considered for use by regulatory and public health authorities in the establishment of population thresholds for peanut. Data should also be gathered on individual NOAELs and LOAELs for other commonly allergenic foods to determine if their threshold levels are similar to peanut. However, lesser amounts of data are likely available than for peanut.

Table 5
ED_{10} and ED_{05} doses for whole peanut as assessed by the log-normal probability distribution model for inclusion of the right-censored subjects in the publications dataset.

Group	Total no. of peanut-allergic individuals	ED_{10}	95% CI	ED_{05}	95% CI
Right-censored[a]	164	14.1	6.6, 29.9	4.2	1.7, 10.1
Non-right-censored[b]	97	6.1	2.8, 13.2	2.2	0.9, 5.4

All values reported in mg of whole peanut.

[a] Nine published studies yielded NOAELs and LOAELs for 164 peanut-allergic individuals, 67 of which were right-censored (see Taylor et al., 2009).

[b] Non-right-censored dataset contains NOAELs and LOAELs for 97 peanut-allergic individuals from the published studies that are either left-censored or interval-censored.

Conflict of Interest

The authors declare that there are no conflicts of interest.

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