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## Regulatory Toxicology and Pharmacology

journal homepage: [www.elsevier.com/locate/yrtph](http://www.elsevier.com/locate/yrtph)

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

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

<sup>a</sup> TNO Earth Environmental and Life Sciences, Zeist, The Netherlands

<sup>b</sup> Coca-Cola Services, Brussels, Belgium

<sup>c</sup> Safety and Environmental Assurance Centre, Unilever, Colworth House, Sharnbrook, Bedford, UK

<sup>d</sup> King's College London, Department of Psychological Medicine London, UK

<sup>e</sup> International Life Sciences Institute – ILSI Europe, Brussels, Belgium

<sup>f</sup> Berlin, Germany

<sup>g</sup> TNO Healthy Living, Zeist, The Netherlands

<sup>h</sup> TNO Triskelion, Zeist, The Netherlands

### ARTICLE INFO

#### Article history:

Received 17 May 2010

Available online 15 September 2010

#### Keywords:

Food allergy  
Public health  
Scientific criteria  
Framework  
Soybean  
Milk  
Peanuts  
Lupine  
Buckwheat  
Sulfites

### 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.

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### 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](mailto:publications@ilsieurope.be) (J.H.M. van Bilsen).

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

<sup>a</sup> 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 <sup>a,b</sup> 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 <sup>a</sup> , and with IgE antibodies	2a
	As above, but not confirmed by DBPCFC <sup>a,b</sup>	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
		4
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

<sup>a</sup> Double-blind placebo-controlled food challenge.

<sup>b</sup> 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 <sup>a</sup> , demonstrating the presence of bound IgE antibodies and/or a positive SPT <sup>c</sup>	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 <sup>c,d</sup> studies in well-characterized <sup>a</sup> patients, with defined doses of specific food <sup>a</sup> in well described matrix <sup>f</sup> and with specific bound IgE antibodies and/or a positive SPT	1
	Series of patients with well-documented <sup>d</sup> history of reactions to suspected food, confirmed or not by DBPCFC <sup>c</sup> , 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 <sup>b</sup> 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 DPBFCF 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 <sup>d</sup>	1
	As above but without DBPCFC <sup>d</sup>	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

<sup>a</sup> Level of details sufficient to be reproducible.

<sup>b</sup> 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.

<sup>c</sup> Double-blind placebo-controlled food challenge.

<sup>d</sup> Or open challenges for infants.

<sup>e</sup> skin prick test, preferably performed according to the accepted guidelines.

<sup>f</sup> 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

**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.				

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.

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) Mittag et al. (2004b)				X
Milk	Saarinén et al. (1999) Schrandt et al. (1993)	X			
Lupine	Moneret-Vautrin et al. (1999) 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) Grundt et al. (2002)	X			
			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 (García-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			
	1	2	3	4
<i>IgE-mediated mechanisms</i>				
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			
<i>Adverse reactions caused by IgE-mediated reactions</i>				
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			
<i>Potency</i>				
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		
<i>Severity</i>				
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
<i>Prevalence</i>				
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.

## Acknowledgments

This work was commissioned by the Food Allergy Task Force of the European branch of the International Life Sciences Institute (ILSI Europe) and the Food Safety Program Management of TNO Quality of Life. The work was financially supported by a grant from the ILSI Research Foundation and Knowledge Program funding by Dutch Ministry of Health, Welfare and Sport. Industry members of the Food Allergy Task Force are: Barilla G. & R. Fratelli; Bayer CropScience BioScience; Coca-Cola Europe; Danone; H.J. Heinz; Kraft Foods Europe; L'Oréal; Mars; Nestlé; PepsiCo International; Tereos-Syral and Unilever. The Expert Group member R. Crevel is author of both this manuscript and Björkstén et al. (2008). The work of the Expert Group and its publication was coordinated by Fiona Samuels, Scientific Project Manager at ILSI Europe.

For further information about ILSI Europe, please email [info@ilsieurope.be](mailto: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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