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Criteria for identifying allergenic foods of public health importance

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Abstract

The World Health Organisation and other food safety authorities recognise food allergy as a significant public health concern due to the high prevalence and potential severity of the condition and the impact it has on the quality of life and economy. A public health perspective focuses on risk management at the societal level rather than precautions taken by individuals. Allergen lists were originally drawn up on the basis of a combination of prevalence and severity information, but data to document inclusion were limited. Since then the number of allergenic foods for which reactions have been well documented has grown considerably. Yet, most of them are of limited significance to public health.

To address food allergy issues from the point of view of risk management, an expert group appointed by the Food Allergy Task Force of the International Life Sciences Institute ILSI Europe reviewed the criteria. We propose a revised set of criteria together with a framework which can be used to help decide which allergenic foods are of sufficient public health importance to be included in allergen lists. Criteria include clinical issues (diagnosis, potency of allergen, severity of reactions), population elements (prevalence, exposure) and modulating factors (food processing). In the framework, data providing evidence for these criteria are weighted according to quality, using a ranking derived from evidence-based medicine. The advantage of this approach is that it makes explicit each of the considerations, thereby rendering the whole process more transparent for all stakeholders.

Keywords: Allergenic foods; Criteria; Risk; DBPCFC; Public health

1. Introduction

IgE-mediated food allergy is a significant public health issue because of the number of people affected and the severity of the reactions. Food allergy is generally estimated to affect about 2% of adults and 4–8% of children (EFSA, 2004) although some recent studies in Europe (Moneret-Vautrin and Morisset, 2005) and the USA (Sampson, 2004; Sicherer et al., 2004) suggest a higher prevalence. Many foods have the potential to be allergenic and a large number (in excess of 160) have been reported to provoke allergic reactions in sensitive individuals (Hefle et al., 1996; Bush and Hefle, 1996). The actual number of

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allergenic foods of clinical importance is much lower and those relevant to public health are often limited to fewer than a dozen food groups (Bousquet et al., 1998; Food and Agriculture Organisation, 1995). Public health relevance of allergenic foods depends not only on national sensitisation patterns, but also on consumption habits.

The need to avoid an allergenic food requires care when buying food and preparing meals. Extreme precautions may be taken for fear of a potentially severe reaction caused by the accidental intake of an allergenic food. As a consequence, food allergy may significantly reduce the quality of life of sufferers and their families and lead to nutritional deficits. Indeed, some food-allergic individuals experience a lower quality of life than even patients with chronic conditions, such as Type 1 diabetes mellitus (Avery et al., 2003; Bock et al., 2001; Cohen et al., 2004).

The 'cost' of risk management measures and public interventions, whether economic or social, is considerable. It is therefore imperative that any measure implemented be targeted and effective. Adding foods to an allergen list has implications beyond the cost of compliance. It also leads to the inclusion of those foods in food operators' allergen management plans, and likely an increase in precautionary labelling. Extensive precautionary labelling of food products is not helpful to food-allergic persons and may even increase the risk of a reaction, as the allergic individual may become less observant of real hazards if many foods routinely carry warning labels.

This paper proposes a way to evaluate the scientific literature on food allergy from a public health perspective and suggests a decision-making framework as a tool for risk management. The framework should be applicable globally and be suitable for risk managers in both regulatory bodies and industry. Risk assessment and risk characterisation are well described for other scientific disciplines, for example, toxicology, but it is recognised that special considerations may apply for food allergens (Barlow et al., 2002).

The proposed framework would improve risk management, facilitate a dialogue among stakeholders, optimise consumer choice and allow a transparent basis for risk assessment and mandatory allergen labelling. A key feature of the framework is that available evidence is analysed, employing criteria developed for evidence-based medicine. The paper addresses only IgE-mediated food-allergic reactions, as such adverse reactions are potentially very severe and can even be life threatening. The potential for a food to sensitise an individual is not discussed, nor are food-induced adverse reactions which are not IgE mediated.

2. Risk assessment considerations for food allergy

As discussed already, over 160 foods have been reported to provoke allergic reactions, some in extremely rare instances (Bousquet et al., 1998; Food and Agriculture Organisation, 1995). It is clearly impracticable, as well as unnecessary, to manage the risk from all these foods on the same basis and prioritisation is therefore required. Risk assessment provides a widely accepted basis for this prioritisation.

The process of risk assessment is conventionally broken down into four separate stages: hazard identification, hazard characterisation, exposure assessment and risk characterisation. Risk characterisation brings together data from exposure assessment and hazard characterisation (Barlow et al., 2002). There are several differences between conventional toxicological risk assessment and risk assessment for food allergens in relation to triggering of reactions. Only individuals in the sensitised sub-population of consumers will be affected by food allergens. Even within this sub-population there is an individual variation of several orders of magnitude in the dose of food allergen necessary to trigger a reaction, depending on factors like genetic predisposition lifestyle, medication and dietary factors, and last but not least degree of sensitisation (Taylor et al. 2002; Sicherer, 2000). It is difficult to measure the "No Observed Adverse Effect Level" in the population. Issues include study design, individual variability, inconsistent definition of 'adverse' reactions, nature of the challenge food, the ability to hide the allergen and the number of potential allergens in question. To address these issues a large number of subjects would be required (Dorato and Engelhardt, 2005; Kroes et al., 2000; Ballmer-Weber et al., 2007). Additional considerations are replication of real life exposure conditions in the challenge study (e.g. environmental factors, alcohol, exercise, medication, etc.), and lack of representation of the entire allergic population by the study group where highly sensitive individuals are usually excluded. Lack of knowledge of the prevalence of a particular food allergy in the population poses further problems. Information regarding incidence (the number of new cases of food allergy reactions in a population over a specific period of time) and prevalence (the number of individuals in a population with a certain food allergy at a specific time) can be obtained from many sources, including epidemiological studies, clinical reports, allergic reaction registries and telephone surveys (Pearce et al., 2000; Selnes et al., 2005; Ellison-Loschmann et al., 2004; Thompson and Belsito, 2002). The quality of data obtained from these sources varies considerably, however, and risk managers therefore often have to make decisions based on proxy indicators.

In evidence-based medicine, available evidence from several disciplines, e.g. clinical medicine, epidemiology, allergology and food technology, is assessed and weighted, based on the quality of evidence, relevance and statistical power (Oxford-Centre for Evidence Based Medicine, Homepage on the internet). The various pieces of evidence are given relative weights ranging from a score of 1 for strongest data confirmed by several properly designed studies, to a score of 5 for merely an expert opinion based on limited data or theoretical considerations (see Table 1, for an overview).

An element to consider in judging the public health importance of food allergy is how easily the adverse effect

Table 1
Examples of evidence from studies of food allergy in relation to criteria employed in Evidence-Based Medicine to assess strength of evidence

Level of evidence	Type of evidence	Examples of evidence from studies of food allergy
1a	Systematic review of controlled trials	Systematic review of 1b DBPCFC[a] studies
1b	Single controlled trial (with narrow confidence interval)	DBPCFC studies in well-characterised patients, with defined doses of specific food
2a	Systematic review of cohort studies	Systematic review of good quality case series
2b	Individual cohort study	Case series of documented reactions to suspected food, confirmed by DBPCFC, and IgE antibodies
2c		As above, but not confirmed by DBPCFC
3a	Systematic review of case-control studies	Case reports confirmed by specific IgE to suspected food, but not DBPCFC
3b	Individual case-control study	
4	Case series (and less convincing cohort and case-control studies)	Anecdotal case reports of reactions to a food, not confirmed by IgE, but with symptoms consistent with IgE-mediated reactions
5	Expert opinion without explicit critical appraisal, or based on physiology, bench research or first principles	Hypothesis formulated about the allergenicity of a food because of its similarity to a food the allergenicity of which has been documented

Adapted from: http://www.cebm.net/index.asp. The types of studies related to food allergy are roughly equivalent to the evidence employed in Evidence-Based Medicine.
[a] Double-Blind Placebo-Controlled Food Challenge.

can be avoided by measures taken by the individual, and whether measures taken by the society are necessary or the most efficient way to prevent adverse effects. Current regulations in many countries stipulate mandatory allergen labelling as a risk management measure for a relatively small number of allergenic foods. The criteria used to decide which foods should be subject to labelling and other measures have never been explicitly defined, however. Mandatory allergen labelling came fully into force in the EU in November 2005 (Anonymous, 2003), while similar legislation in the USA has been applied since January 2006 (USA Food and Drug Administration, 2004). Many other national governments already have operational labelling legislation.

3. Criteria for identifying allergenic foods of public health importance

3.1. General aspects

In 1995, a Food and Agriculture Organisation/Codex Technical Consultation identified eight food groups as the most common causes of IgE-mediated food allergy worldwide (Food and Agriculture Organisation, 1995). The main criterion for inclusion was the frequency of reported reactions, although this remained implicit. In 1998, ILSI Europe reviewed the list and critically evaluated the quality of evidence for allergenicity (Bousquet et al., 1998). Two key criteria were proposed, i.e. allergenicity as confirmed by properly conducted double-blind-placebo controlled food challenge (DBPCFC) studies, and severity of the reactions. Thresholds for eliciting doses and processing factors were recognised as important, but could not be included due to the lack of data at the time.

Fig. 1 outlines the proposed framework and the criteria that should be considered to decide whether a food allergen is of sufficient public health importance to warrant mandatory risk management measures. Some of the outlined criteria depend on each other although the link is often poorly understood. There is, for example, no clear individual relationship between allergen-specific IgE level, allergen exposure and adverse clinical reaction (Østerballe and Bindslev-Jensen, 2003) although for a limited number of allergens, IgE levels may predict the outcome of a DBPCFC (Perry et al., 2004). Nevertheless, quantity and quality of data for most of the different criteria that are available for risk management vary greatly.

3.2. Verification of diagnosis and severity

The first two criteria proposed are to confirm that a food may cause an IgE-mediated reaction and the severity of reaction. The different types of available clinical data and the weight they should be given, based on their quality, are described in Table 2. These are assessed using a scoring system adapted from the criteria used in Evidence-Based Medicine (Table 1). The first indication that a certain food is allergenic usually appears as isolated case reports. These reports should ideally include a DBPCFC undertaken according to a recognised protocol, e.g. as suggested by the EAACI in 1995 (Bruijnzeel-Koomen et al., 1995), as this is a prerequisite to confirm a causal relationship between a clinical reaction and the intake of a suspected food. Further serological evidence would then be required to confirm that the observed adverse reactions are IgE-mediated.

The observed clinical symptoms can provide information regarding the severity of the reaction (for description of clinical grades of adverse reactions see Brown, 2004). Even in the absence of a DBPCFC, it may be possible to extract some evidence about the potency of the allergen if information about the amount that provoked the reaction

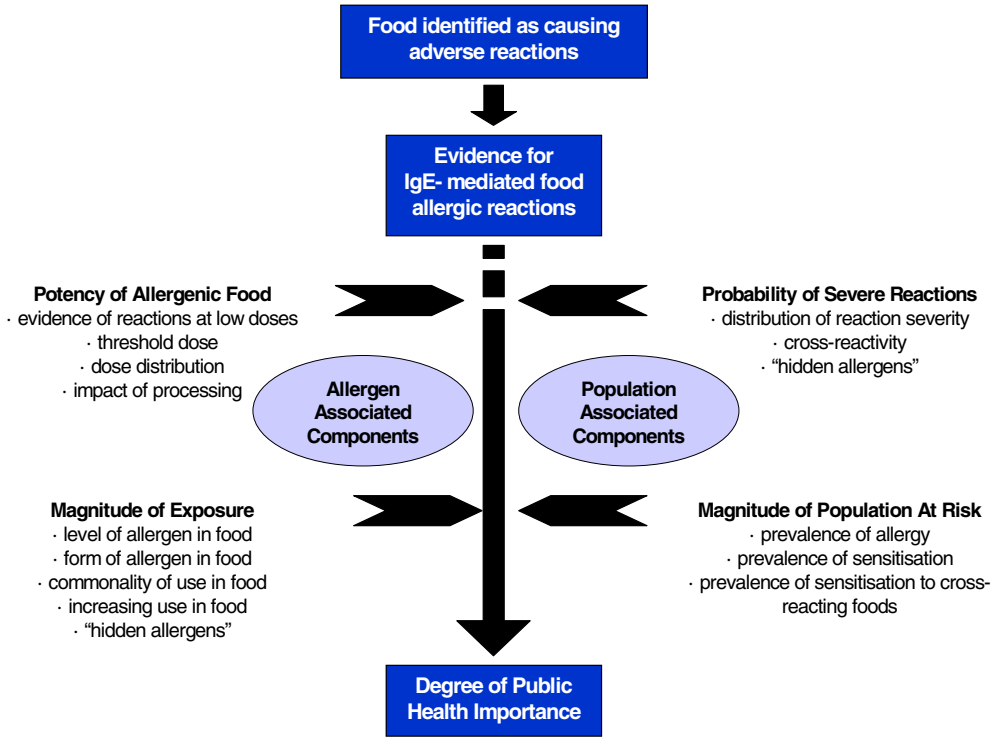

Fig. 1. Framework of criteria employed to identify allergenic foods of public health importance.

Table 2
Type and level (weight) of evidence of clinical data in IgE-mediated food allergy

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 characterised	3
Adverse reactions caused by IgE-mediated reactions	Systematic DBPCFC[a,b] studies in well-characterised 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

Both criteria below should be met, i.e. that a food can cause the formation of IgE antibodies and that an adverse reaction to food is caused by an IgE-mediated reaction.

[a] Double-Blind Placebo-Controlled Food Challenge.

[b] And open challenges for infants.

is available (Malmeheden-Yman et al., 1994). Other potential causes for a reaction, e.g. reactivity to another food ingredient or to a trace of an unlabelled allergen, must also be excluded (Gern et al., 1991; Laoprasert et al., 1998).

Multiple case reports from several independent clinical centres would strengthen the notion that the food is indeed likely to be a food allergen of public health importance. Assessing clinical data from different geographical regions will also be useful for evaluating the relative frequency of reactions to different allergens and will thus provide a proxy measure for prevalence (see later section on prevalence).

3.3. Allergenicity

Most foods are complex products, but only some proteins in the food are of relevant potential allergenicity. Furthermore, only small parts of the proteins comprising a few amino acids are reactive. Individuals who are allergic to, for example, milk may react to different proteins or to dif-

ferent epitopes on the same protein. As a consequence, there are large individual variations in the allergic response pattern, even to the same food. The issue is complicated by the variability of the food itself. Thus, different cultivars of, for example, apples or species of fish may contain different amounts of allergenic proteins (Sancho et al., 2006; Wilwert et al., 2006). Environmental factors, such as growth conditions, ripeness and storage conditions, may further modify allergenicity. The term allergenic potency can either be understood as the amount of an allergenic food required to sensitise an individual, or as the amount of food required to elicit a reaction in an already sensitised individual. In this paper, the amounts provoking adverse reactions are considered. This is because risk management of common allergens aims to reduce the probability of adverse reactions in allergic individuals, rather than preventing them from becoming allergic. Potency can be described either as the "frequency dose–response" defined as the population distribution of doses eliciting or provoking a reaction, or as the "severity dose–response" denoting the gradient of severity of reactions caused by the food. Both definitions are relevant to consider for public health. It may be difficult, however, to directly compare the public health impact of foods causing relatively mild but frequent reactions affecting a large number of the population from other foods causing very severe reactions in a few individuals.

Minimum eliciting doses (MED) for various food allergens can be determined in clinical studies by serial challenge studies, starting with very low doses (Table 3). It can however be difficult to recruit a sufficient number of human subjects, who are representative of the allergic population as a whole. The eliciting dose (ED) at which 5% (ED_5) or 1% (ED_1) of the population would be expected to react (see Fig. 2 for an illustration) could be estimated by mathematically fitting dose–distribution curves (Crevel et al., 2007).

The relationship between dose and severity of reactions is largely unknown. In a chart review of 538 diagnostic challenges, Perry et al. (2004) found that mainly doses over 100 mg were linked to severe reactions. However, a number of other studies and case reports indicate that severe reactions may occur well below 100 mg (EFSA, 2004; Bindslev-Jensen et al., 2002; Taylor et al., 2004a). Thus, it is currently not possible to define an absolute minimum eliciting dose (MED) (i.e. a population NOAEL) for severe reactions for most allergenic foods. Data on MEDs for severe reactions are likely to remain scarce and difficult to obtain, given that they effectively rely on inadvertent ingestion or errors in controlled challenges. The best data available to the risk assessor will likely remain MEDs for any reaction (i.e. mild reactions) as observed in low dose challenge trials. Several groups, including ILSI, are developing predictive dose–distribution modelling using such data (Taylor et al., 2002).

The potential for allergenicity is determined by the amount of protein and derived peptides present in the end product (Taylor and Hefle, 2001). For instance, highly refined soybean oil can be considered relatively safe for

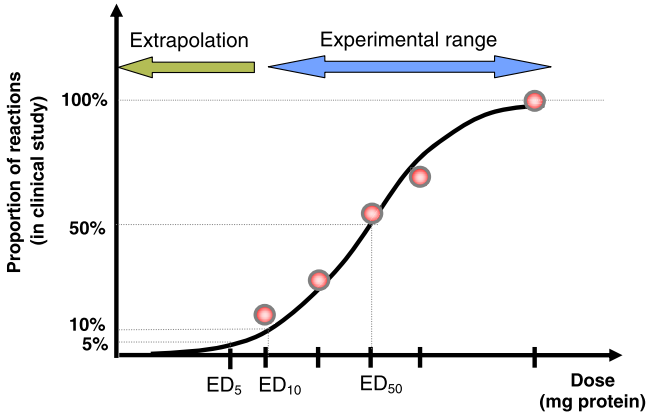

Fig. 2. Illustration of the generic relationship between dose of allergenic protein and frequency of adverse reactions in clinical challenge studies. A theoretical eliciting dose (ED) can be extrapolated from the graph of experimental responses to a range of standard challenge doses.

Table 3
Type and level (weight) of evidence for allergenic potency, severity of reactions and prevalence

	Type	Level
Potency	Threshold studies with good range of doses and adequate numbers of well-characterised 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

soybean-allergic individuals (Bush et al., 1985, Taylor SL, unpublished information) as no or very low levels of protein are still present (Crevel et al., 2000). The nature of the protein from the allergenic source can also be significant. Fish gelatin is a collagen-based protein product derived from fish which has been shown to be safe for cod-fish-allergic individuals up to gram intakes (Taylor et al., 2004b; Hansen et al., 2004).

Food processing often reduces, but may sometimes enhance, allergenic potency (Wal, 2003; Fiocchi et al., 2004a) by denaturation, deamination or by changing the chemical structure of proteins. Changing the folding structure can uncover or create new epitopes (Davis et al., 2001). Some examples of heat stable proteins include those from milk, egg, fish, crustaceans, peanut, soy. Other allergenic proteins become more labile from heating or breakdown in the digestive tract, for example, pollen related allergens present in celery (Ballmer-Weber et al., 2002) and hazelnut (Vieths et al., 1998).

3.4. Prevalence and incidence

The prevalence in a population is determined by studies in representative population samples. Clinical trials are of limited value in this respect, as they are done in groups of patients from which it is difficult to draw quantitative conclusions about the whole population. They do however provide information regarding levels and ranges of sensitivity among certain individuals, as well as severity of allergic reactions, and can be used to rank allergenic foods.

The prevalence of sensitisation is usually established by the presence of positive skin prick tests (SPT) and/or allergen-specific serum IgE antibodies in representative population studies. However, since many diagnostic reagents used *in vitro* and *in vivo* for the detection of IgE antibodies to foods are poorly standardised and lack sensitivity and possibly specificity, estimates of the prevalence may be incorrect. It should also be noted that the relationship between sensitisation and clinically manifest food allergy is not direct (Sampson, 2004). Thus, a number of individuals with IgE antibodies tolerate well foods to which they are sensitised.

Estimates of the prevalence of food allergy across the population can be based on: (a) self-reports of allergy, (b) physician-diagnosed allergy based on clinical history and (c) DBPCFC and presence of IgE antibodies studies in a representative population sample (Østerballe et al., 2005). Often these approaches are used in combination. DBPCFC with confirmatory presence of IgE antibodies specific for the challenge allergenic food is the most accurate and definitive evidence, but it is difficult and expensive to employ in large studies. Therefore, only a few such studies have been undertaken, for example, in U.K. (Young et al., 1994), Denmark (Fuglsang et al., 1993) and Germany (Zuberbier et al., 2004). Currently available information regarding most allergenic foods is therefore based on selected populations studied in clinical centres. Such data do not provide accurate information on the prevalence in the general population, however.

Self-reported data on food allergy are often considered to be less reliable and to grossly overestimate prevalence. Rona and co-workers very recently performed a meta-analysis of published prevalence studies (Rona et al., 2007). Out of 934 retrieved articles that were related to the prevalence of food allergy, only 51 met the inclusion criteria. The authors could confirm that the prevalence of self-reported food allergy was high as compared with objective measures, i.e. IgE antibody determinations and provocation tests. There was a marked heterogeneity between studies which persisted after age stratification. The study underlines the difficulty in obtaining reliable prevalence data that could be employed in different populations. However, recent validations of telephone survey data suggest that this overestimation is now no more than by a factor of 2 (Sicherer et al., 2003, 2004), as compared to 10-fold overestimates reported in earlier studies (Young et al., 1994). Well-conducted telephone surveys thus probably provide better estimates of food allergy prevalence than SPT and serum analyses. Table 3 describes sources of prevalence data and assigns weight to the different types of evidence.

3.5. Risk characterisation

The range of sensitivity to any food allergen is very wide within a population (Wensing et al., 2002a,b). The vast majority (>95%) are not allergic at all and will not suffer an allergic reaction regardless of the amount consumed. Most allergic individuals are only moderately sensitive, while a small number will be extremely reactive and may experience anaphylactic reactions upon exposure to even very low amounts (Wang and Sampson, 2007). Each individual will vary in their allergic minimum eliciting dose (the amount of allergen reported to provoke a reproducible allergic reaction in an individual) over time and with circumstances. Thus, sensitivity may increase due to infections, illness (particularly poorly controlled asthma), stress, alcohol, certain medication, exercise and possibly hormonal factors, but this has not been proven. The matrix in which the allergen is present may also affect the responsiveness of some individuals, possibly by altering the kinetics of release from the food. For unknown reasons, sensitivity diminishes with time in many individuals, while in some persons it may increase.

3.6. Exposure

Inadvertent exposure to allergens can occur in one of two principal ways, either through deliberately added ingredients, which are not labelled, or through allergen present adventitiously through operations in the supply chain. Most legislation specifically directed at allergens aims to ensure that deliberately added allergens are always declared, but risk managers must also consider adventi-

Table 4
Factors to consider when assessing risk of exposure to an allergenic food

Use of food	Common, rare, new use
Form of allergen in food	Hydrolysed, denatured, native
Amount of protein and derived peptides present in ingredient	Analytical studies on representative samples establishing level of allergen/amount of protein or derived peptides present in ingredient
	Impact of refining process
Evidence of impact of processing	Increase or decrease potency of allergen
	Generation of neo-allergens
'Hidden' allergen	Not easily recognisable as a constituent of the food
	From inadvertent cross-contact
Cross-reactivity	Allergen present in a food that cross-reacts with an allergen to which the consumer is sensitive

tious exposure. Table 4 provides a non-exhaustive list of exposure considerations.

Allergic individuals will react if they are exposed to an amount of allergenic food exceeding their personal threshold. The risk assessment needs to focus on the amount ingested on a single occasion, rather than continuous exposures to low doses in contrast to classical risk assessment for other food constituents. The per capita consumption and the total number of consumers will affect the potential number of reactive individuals and are therefore important for risk management. More significant and challenging to the risk manager is ensuring that an allergic individual can avoid exposure to the allergen in question, avoiding unexpected or inadvertent presence in a food.

Adventitious or "hidden" exposure relates to the unexpected presence of an allergen in a food product which the individual may be unfamiliar with. For example, milk, soy, wheat or egg protein may be present in a meat sausage or casein may be used as a binder in canned fish. Additionally, novel ingredients may be substituted for a traditional one, for example, lupin and pea proteins used as soy replacers. The inadvertent presence of an allergen may also be due to cross-contact occurring at any point in the supply chain (Heckmann et al., 1992; Foucard and Malmheden-Yman, 1999; Leduc et al., 2003; Malmheden-Yman, 2004; Koppelman et al., 1999).

In contrast, some allergenic foods, for example, fruits such as peach, kiwi and apple, are normally easily recognised and do not require labelling or other risk management strategies. Although some fruits can cause severe reactions and contain heat stable allergens, for example, in fruit concentrates (Fiocchi et al., 2004b; Fernandez-Rivas et al., 1997) exposure can be avoided easily because they are either visually recognised or they are labelled due to labelling requirements. As such they do not come within the scope of this paper.

Issues of cross-reactivity complicate assessments of exposure as allergic reactions could be triggered by the ingestion of a cross-reacting allergen. Allergenic epitopes on proteins in different foods can be so structurally similar that the same IgE antibodies recognise them. For example, epitopes of parvalbumin from various species of fish, tropomyosin from different crustaceans, molluscs and mites (Scharer et al., 2002; Martinez et al., 1997; Aki et al., 1995; Asero et al., 2000) and profilins (Guilloux et al., 1998; Breiteneder and Ebner, 2000; De Amici et al., 2003) present in pollens and different plant derived foods may all cause an adverse reaction in an individual who was originally sensitised to any of these examples (reviewed in EFSA, 2004). As a result an individual may react to a food which he/she has never eaten before. This cross-reactivity explains why a mite-allergic person may react to snails (EFSA, 2006).

Another recently reported example of cross-reactivity (Magni et al., 2005) is that some peanut-allergic individuals have experienced severe allergic reactions after consumption of food containing lupin flour (Malmheden-Yman, 2004; Hefle et al., 1994; Moneret-Vautrin et al., 1999; Radcliffe et al., 2005; EFSA, 2005). As lupin flour is intentionally used as an ingredient in food manufacture, but is not always required to be labelled by name, it has become an issue for public health concern (EFSA, 2005). In this case, the degree of public health concern is related to the prevalence of peanut allergy in the population exposed to adventitious or "hidden" presence of lupin in processed foods.

4. Application of the criteria

The first stage to assess available evidence is to decide whether the allergen in question does cause IgE-mediated food allergy (Table 2). As described in the clinical section, the level of data available for most suspected foods may only rank a 3 or 4, as clinical reports will probably only include limited numbers of case studies. However, if this criterion is met even at low evidence level, the risk assessment should move forward to evaluate the other criteria described. If on the other hand the clinical criteria are not met, there is no need to evaluate the food further.

The second stage would be to assess all the other criteria and to weight the evidence (Tables 3 and 4). Absence of data supporting any one of the criteria does not automatically exclude the food from being a potential allergen of public health importance.

Deciding on whether a food allergen is of public health concern relies on many factors. In addition to the criteria discussed in this paper, a decision will build on considerations such as how long the food has been on the market and reported history of adverse reactions. Fig. 3 illustrates how the two main factors considered when trying to decide whether an allergenic food is important from a public

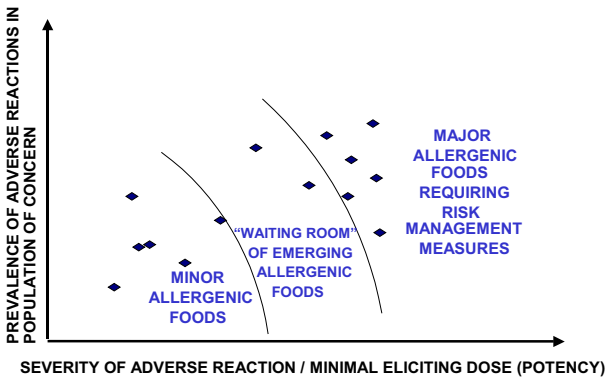

Fig. 3. Theoretical representation of risk assessment grouping when deciding whether an allergenic food is important from a public health perspective. The division into groups is arbitrary. The *y*-axis represents the magnitude of likelihood of an adverse reaction, whereas the *x*-axis represents the magnitude of potency as a ratio of the severity of elicited adverse reaction and the potency of dose required to elicit reaction.

health perspective can influence risk management decision-making. On one hand, a food allergen that commonly causes severe adverse reactions in a population is obviously of public health concern. At the other end of the spectrum are foods that rarely cause any allergic reactions, and if they appear they are mild. The middle section includes foods with high and low scores for the various criteria. It also includes foods recently introduced in the population, for which more information is required. Foods in the lower left of the diagram have low scores for all the criteria and they are not presently public health concerns. The precise line drawn to define a food as an allergen of public health importance will be based on risk management policies and societal perception of tolerable risk.

The data available to support an assessment using the framework and criteria described in the previous sections can be of variable quality and quantity. To illustrate how such a framework for defining allergenic foods of public health importance could be employed, some example data for hen's egg are shown in Table 5. This allergenic food was selected as it is better documented than most other foods. From the data shown it is possible to conclude that the quality of evidence for egg as an allergenic food is convincing. Considering the role of egg in the diet, as an ingredient and food constituent, it is indeed of public health importance. As a well-characterised, and fairly common, allergenic food, egg and protein containing derivatives of egg are subject to mandatory labelling.

5. Concluding remarks

Food allergy is widely recognised as an important public health issue. However, several factors complicate risk assessment and management. Unlike many chemical or microbiological hazards, allergenic foods pose no risk at normal levels of intake to people who are not allergic to them. Many allergenic foods are important constituents of a balanced diet and are widely consumed. The spectrum of sensitivity in the allergic population is very wide, ranging from sub-milligram amounts up to almost a normal portion size. For many of the documented allergenic foods, the number of recorded adverse reactions is very small. Management of the risk associated with food allergens therefore requires prioritisation so that measures can be targeted most effectively. Applying uniform risk management approaches for dealing with all allergenic foods would impose a burden on society without proportional benefits to public health.

We propose a simple and robust framework to identify allergenic foods of public health importance based on application of a series of criteria, each of which has the strength of the supporting evidence weighted dependent on its quality and strength. This approach can support decision-making as to which allergenic foods are of sufficient public health importance, whether risk management measures are appropriate or relevant e.g. mandatory labelling, and can further be used for decision-making about derived products.

Table 5
Example—ranking of quality of evidence for egg as a food allergen of public health importance

Criterion	Evidence	Level of evidence		
		1	2	3
IgE-mediated mechanism	Several clinical studies	X (b)		
Confirmed by DBPCFC	Several clinical and population studies	X		
Prevalence	2.6% ± 1% at 2 years (Eggesbo et al., 2001)	X		
Severity	Severity increase >3.33 mg (Hefle et al., 2003)		X	
Potency	Oral challenge		X (a)	
	MED: 0.03–33.33 mg of whole egg (Hefle et al., 2003)		X (b)	
	1 in 1 000 000 would react to 0.002 mg allergen and 1 in 100 at 0.15 mg of allergen (Bindslev-Jensen et al., 2002)		Modelled data	
Exposure Consumption adventitious	Labelling mandatory	X		
	Some adventitious exposure at low doses is possible			
	73% of product recalls due to egg contamination (USA, 1999) (Vierk et al., 2002)			
Aggravating factors	Egg allergens are heat stable (Bindslev-Jensen et al., 2002)	X		X
	Cross-reactivity possible with other avian eggs (Langeland, 1983)			

The criteria include the demonstration of an IgE-mediated adverse reaction, estimates of the prevalence, severity of reactions, allergenic potency of the food and the extent, pattern and nature of exposure to the food. The scheme also recognises that the protection of public health may mean that decisions need to be taken before sufficient data are available and consequently proposes ways in which the scheme can be adapted to deal with such situations. Systematic and consistent evaluation of the evidence would facilitate dialogue amongst stakeholders and risk manager from different geographical jurisdictions. Potentially allergenic foods that are introduced into a previously unexposed population could be particularly carefully monitored for a period of time in order to avoid premature classification of foods as allergens of public health importance. A list of such emerging allergenic foods would alert clinicians and enable them to be particularly observant and quickly report any suspected severe reactions.

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