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Scientific criteria and the selection of allergenic foods for product labelling

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Introduction

Food allergy is estimated to affect 1–2% of the adult population, and its prevalence is higher in infants and children (1). The most common allergenic foods, worldwide, are egg, milk, fish, crustaceans, peanut, soybean, wheat, and tree nuts (Table 1). These commonly consumed allergenic foods are considered to account for over 90% of food allergies. However, there is a much longer list of other foods and food ingredients that have been associated with allergic reactions in sensitive individuals.

The risk of suffering an allergic reaction is a function of the sensitivity of the individual to the allergen, the potency of the allergen to cause a reaction, and the amount of the allergen (the dose) ingested. If data were available for each of these factors, it would be possible to rank food allergens by potency to cause severe reactions. In this way, important allergens could be identified. They would require careful tracking during food manufacture and food preparation. Their presence in the foodstuff could then be clearly labelled. If it were known that certain food-processing methods inactivate or remove the allergen (to levels well below the threshold known to trigger allergic reactions), then tracking and labelling would not be necessary.

Currently available information on potency and thresholds for food allergens is insufficient to allow such a systematic ranking for all but the more potent food allergens, such as peanut. The definition of major allergens is currently dependent on the results of clinical studies, epidemiologic studies, and the expertise of practitioners in food allergy.

The principal tool available for the food industry to help in the management of the risk of food-allergic reactions is the accurate labelling of products to indicate clearly their composition.

Individuals sensitive to a particular food or ingredient can then avoid consuming the product in question. For this approach to be truly effective, it is essential to have a scientifically validated list of major food allergens, coupled with an understanding of the proportion of food-allergy sufferers reacting to such foods. This targeted approach would enable the food industry to work with clinicians to ensure that initiatives of food-allergy management will be the most effective to reduce the incidence of allergic reactions to foods.

If the decision to classify major food allergens is based solely on the knowledge and experience of practitioners in the field, without the discipline of defined criteria, it is likely to lead to a proliferation of lists in different countries. Moreover, it is possible that certain important candidate foods may not be included on such lists.

Thus, this paper is concerned with outlining the three essential steps to establishment of a list of major allergens, namely:

1) propose scientific criteria to define allergens which would require the foods containing these substances to be labelled
2) evaluate the suitability of the criteria based upon a review of the scientific literature on food allergy
3) determine which food allergens meet the criteria outlined in (1).

This review is a first step in an attempt to define scientifically a list of food allergens for mandatory labelling on the basis of the information that is currently available. Such an approach can help to identify key areas for further research, ultimately leading to improved criteria for redefining the list of major food allergens.

A. Terms of reference and goals

An Expert Consultation of the Food and Agriculture Organization (FAO) of the United Nations was convened in Rome (Italy) in November 1995. A list of the most common allergenic foods was proposed as a draft amendment to the General Standard for the Labelling of Prepackaged Foods (2). This list, as follows, is currently being considered by the Codex Alimentarius Committee on Food Labelling:

1) barley, oats, wheat, triticale, and products of these (gluten and starch included)
2) crustaceans and other shellfish, and products of these
3) eggs and egg products
4) fish and fish products
5) legumes, peas, peanuts, soybeans, and products of these
6) milk and milk products (lactose included)
7) sulphite in concentrations of 10 mg/kg or more
8) tree nuts, poppy seeds, sesame seeds, and products of these.

The objectives of the ILSI Europe Task Force on Food Allergy are as follows:

1) to develop the scientific support necessary to underpin the listing of major food allergens. The list of the FAO is the starting point but other foods have been considered (e.g., celery, Prunoideae fruits). Although included in the FAO list, sulphites were not considered by the task force because studies have shown that this form of food intolerance occurs by an unknown mechanism, and most sulphite-sensitive asthmatics can tolerate small quantities of sulphites with no ill effects (3).
2) to assess the possibility of determining threshold doses for food allergens
3) to determine whether food processing may alter the allergenicity of the foods.

B. Diagnosis of food allergy

While allergic reactions to foods are usually due to IgE-mediated hypersensitivity reactions, a number of immune mechanisms may contribute to adverse reactions to foods that have an immunologic basis. Tests for IgE antibodies include both skin prick tests (SPT) and the measurement of serum allergen-specific IgE antibodies. The diagnosis of food allergy is complicated, however, because the allergen extracts and test reagents currently available are not standardized, and their stability is poorly determined (4). For allergen extracts that are rapidly degraded, such as those of fruits, skin tests may be falsely negative in allergic individuals and skin tests with raw foods are preferred. The presence of food-specific IgE in serum or a positive skin test to a foodstuff does not always correlate with a food allergy since:

1) many patients outgrow their allergy with age (5, 6)
2) not all patients with food-specific IgE have clinical sensitivity
3) most reagents are as poorly standardized as those used for skin prick tests.

Often, the diagnosis has to be confirmed by a double-blind food challenge, which should be carried out under precisely specified conditions by trained staff who are competent to manage and reverse anaphylactic reactions. As for other forms of allergy, unproven and controversial techniques such as cytotoxic tests or sublingual provocation tests have no proven value.

Food challenge tests are an important diagnostic tool for supporting diagnosis. They should be performed as a double-blind, placebo-controlled food challenge (DBPCFC) (7, 8). It is generally accepted that patients who have presented with anaphylactic symptoms to a particular food should not be tested. The positivity of DBPCFC may be assessed by symptom scores or objective measures such as forced expiratory volume in 1 s (FEV_1) (9). For eczema, some scoring systems are of proven value (SCORAD) in assessing the response (10). For overall symptoms, a combined clinical score may be used (11). It has also been observed that food challenges increase nonspecific bronchial hyperreactivity to histamine or methacholine without causing frank wheezing or fall in FEV_1 in some (12, 13), but not all, studies (14).

C. Criteria for selection of foods

The current state of knowledge allows only two scientifically based criteria to decide whether a food should be included on a major allergen list. That is, the food was shown to be positive in a DBPCFC and to cause an anaphylactic reaction. In the future, thanks to the results of further research, it may be possible to identify additional criteria; e.g., sound prevalence data for severe reactions to particular allergens.

At present, some foods have been shown to induce either a positive DBPCFC or an anaphylactic reaction. However, there are some confounding factors which make it difficult to decide whether to select them for inclusion on a list of allergens, and a single case of anaphylaxis may not be sufficient to justify including the food in the list. One confounding factor which is important to consider is the stability of allergens during food processing.

The following criteria to assess the severity of allergic reactions were defined on a scale modified from allergic reactions to Hymenoptera stings (15):

- local reactions
- symptoms of the oral allergy syndrome and "bad" taste
- systemic reactions:
  - I. mild systemic reaction
    generalized urticaria
    pruritus
  - II. moderate systemic reaction
    angioedema
    dyspnoea
    abdominal pain, diarrhoea
    nausea, vomiting
    vertigo
  - III. severe systemic reaction
    severe diarrhoea in infants
    abdominal pain as part of other signs
    dyspnoea with wheezing
    dysphonia
    confusion
    tachycardia
  - IV. life-threatening systemic reaction
    anaphylactic shock
    severe angioedema with breathing difficulties and/or cyanosis
    hypotension
    dyspnoea with wheezing and cyanosis
    syncope
    loss of consciousness.

D. Criteria for selection of papers

The scientific support for the list of food allergens is based on a compilation of the literature for the foods listed by the FAO together with some additional foods. The following criteria were used by the ILSI Europe Task Force members for selection of papers acceptable for review:

1) published in a peer-reviewed journal.
2) in English or a full translation available.
3) where possible, abstracts, posters, oral presentations, personal communications, and reviews were avoided.
4) food was clearly defined. Inhalation and occupational allergy were excluded, but examples could be used to support the conclusions.
5) methodological criteria. Although papers were not selected according to the "evidence-based medicine" methodology (16), they had to include at least:
   - demographic characteristics of the patients studied
   - underlying disease(s)
   - adequate methodology for DBPCFC.
6) defined allergic reaction:
   - nonanaphylactic symptoms (grades I–III)
   - life-threatening anaphylaxis (grade IV).

E. Foods listed in the FAO Expert Consultation

1. Cereals which contain gluten, i.e., wheat, rye, barley, oats, spelt, or their hybridized strains and products of these

Cereals including gluten were included in foods listed in the FAO consultation primarily because of their role in gluten-sensitive enteropathy, otherwise known as coeliac disease. Gliadin, the 70% alcohol-soluble fraction of gluten, is the component responsible (17). The acute reaction of the intestinal mucosa to gliadin in patients with coeliac disease consists of an infiltration of the mucosa by eosinophils and neutrophils, accompanied by oedema and an increased vascular permeability. With time, the infiltration evolves into predominantly mononuclear cells, plasma cells, and lymphocytes (18). Blunting of the mucosal surface, villous atrophy, and a dense infiltration of the lamina propria by plasma cells, B cells, and T cells are observed in chronic disease. Not all cereals contain gluten. Rice and corn (maize) do not contain gluten. Coeliac disease is a cell-mediated reaction not associated with acute, life-threatening effects. Information on the gluten content of foods is essential for coeliac sufferers but is not considered further in this review.

The following section is aimed at reviewing the available data to determine whether these cereals (wheat, barley, rye, oats, spelt, or their hybridized strains) also possess the attributes of a food allergen capable of provoking IgE-mediated reactions with regard to the criteria under Section C (criteria for selection of foods).

1.1. Double-blind, placebo-controlled studies

In a DBPCFC study carried out with wheat in nine children with atopic dermatitis, three of the children showed positive reactions, and there was 40% agreement with the SPT for wheat (19). In a study of 113 children with atopic dermatitis, five of 23 challenges were positive for wheat (20). In a study of 46 children with atopic dermatitis, two of nine challenges were positive for wheat (21).

Challenges with the more common cereals were performed in 145 subjects (22). Eighty per cent of subjects reacted to only one grain. DBPCFC were positive in 26 of 126 challenges with wheat, four of seven challenges with rye, four of 12 challenges with barley, and five of 29 challenges with oats.

A case of asthma caused by wheat ingestion has been confirmed by positive DBPCFC (23).

No data on thresholds for oral challenge are available.

1.2. Anaphylactic reactions

Anaphylaxis to wheat has been reported (24), including one reaction in an infant (25). Exercise-induced anaphylaxis has been documented in wheat (26–28) and gliadin allergy (29).

1.3. Antigenic composition of wheat

Four main groups of wheat proteins have been identified: water-soluble, salt-soluble, alcohol-soluble, and alcohol-insoluble (30, 31). IgE antibodies were found in response to all these fractions; the highest scores were obtained with the globulin fraction, followed by glutenin (31). Recently, two major allergens of wheat have been recognized in studies of subjects (22) who lacked signs of grass-pollen allergy and showed positive DBPCFC to wheat: two water-soluble proteins (47 and 20 kDa) were identified. The identification of the major food allergens of wheat, however, still needs to be confirmed in larger population studies of subjects who lack sensitization to grass pollen and have positive DBPCFC with wheat. The high number of false-positive skin and serologic tests for wheat, about 80%, is probably due to the presence of IgE to grass pollen in atopics.

Wheat α-amylase inhibitor is a relevant allergen in patients experiencing hypersensitivity reactions after the ingestion of wheat protein (32).

So-called hypoallergenic wheat has been produced by preparing enzyme-fractionated wheat-antigenic proteins (33, 34). The efficacy of such preparations has been reported in the Japanese literature (35). With antibodies raised against major food allergens, it is possible to screen for plant strains containing low amounts of a major allergen; e.g., the 27-kDa wheat albumin (36). Such screening methods make it possible to select "low-allergenic" strains.

1.4. Conclusions

1) DBPCFC studies have demonstrated that wheat and, to a lesser extent, certain other cereals can cause allergic reactions.
2) Life-threatening reactions have been observed.
3) The amount of allergen required to induce allergic symptoms has not been identified.
4) Processing does not destroy the allergen present in wheat.
5) The inclusion of wheat on a list of food allergens for labelling is appropriate.
6) Further research is needed to determine the dose required to elicit a severe allergic reaction and to assess whether other cereals induce anaphylactic reactions.

2. Crustacea, other shellfish, and products of these

"Crustaceans" include the Crustacea but not molluscs. Crustaceans have no backbone; their body is divided into sections, each bearing a pair of jointed legs. An armour-like shell covers and protects the body. Included in the classification are shrimps, crayfish, crabs, and lobsters (37). Molluscs include bivalves (clams, oysters, mussels, and scallops), snails, octopus, squid, and *Sepia* (cuttlefish) (37).

Food allergy to crustaceans has been recognized for many years.

2.1. Crustaceans

2.1.1. Double-blind, placebo-controlled studies. Daul et al. (38) carried out DBPCFC studies with shrimp in 30 adults who had symptoms suggestive of food allergy. Twenty-three patients had a positive skin test with shrimp, but only six had a positive DBPCFC. The amounts of shrimp administered in this challenge varied from 1 to 16 shrimp equivalents (4–64 g). No anaphylactic shock occurred during the challenge. However, lower amounts of shrimp may also induce allergic symptoms, and new challenge studies should be carried out for better assessment of the minimal amount of allergen inducing an allergic reaction.

2.1.2. Anaphylactic reactions. Anaphylactic reactions to crustaceans are well established (39). Yunginger et al. (40) identified seven cases of food-related fatal anaphylaxis in patients aged 11–43 years. All victims were atopic with multiple prior anaphylactic episodes after ingestion of the incriminated food, and one patient was allergic to crab.

2.1.3. Antigenic composition. The major allergen previously designated antigen II or Sa II, and now referred to as Pen i 1, has a molecular weight of 34–36 kDa and is heat resistant (41). The amino-acid sequence analysis of Pen i 1 indicates significant homology with the muscle protein tropomyosin from *Drosophila melanogaster* (42, 43). However, tropomyosin has now been identified as the major allergen in four species of shrimp. Isolated shrimp tropomyosin also binds Pen i 1-specific IgE. Limited proteolysis results in peptides, which retain the IgE-binding activity (42). Tropomyosin is also thought to be the common allergen responsible for cross-reactivity between crustacean species (shrimp, lobster, crab, and crawfish) (42, 43). This antigen also shows IgE cross-reactivity in crustaceans and molluscs (44).

2.1.4. Conclusions

1) DBPCFC studies have demonstrated that shrimp can cause allergic reactions.
2) Life-threatening reactions have been observed and at least one fatal case of crab allergy has been documented.
3) The amount of shrimp required to induce allergic symptoms has not been identified.
4) The major allergen is heat-stable.
5) The inclusion of crustaceans on a list of food allergens for labelling is appropriate.
6) Further research is needed to determine the dose required to elicit a severe allergic reaction in highly sensitive individuals.

2.2. Molluscs

2.2.1. Anaphylactic reactions. Among the molluscs, the cephalopods are a group of great importance as a food source. Carrillo et al. (45) reported seven patients who had symptoms highly suggestive of IgE-mediated reactions after either ingesting squid or inhaling vapours from cooking squid. Skin prick tests and IgE were positive for boiled squid extract. Cross-reactivity between squid and shrimp and other crustaceans was demonstrated. Cross-reactivity could not be demonstrated between squid and octopus, which are both cephalopods, nor between squid and other molluscs.

Allergy to another mollusc, limpet, was reported in two atopic patients who developed anaphylactic reactions after ingesting it (46). Positive results for skin tests, specific IgE, and histamine release to cooked limpet extract were found.

Morikawa et al. (47) (subsequent study by Maeda et al. [48]) reported 11 cases of patients who developed moderate to severe anaphylactic reactions induced by the ingestion of grand keyhole limpet and abalone. Specific IgE-mediated hypersensitivity to these shellfish was demonstrated by history, skin prick test, RAST, and immunoblotting.

Carrillo et al. (49) reported six subjects who developed severe bronchospasm 30–120 min after eating limpets. Positive skin tests and IgE were found.

Allergy to molluscs is probably due to cross-reactive antigens, and reports of clinical cases have been published, but this allergy has to be confirmed by DBPCFC. Molluscs can induce anaphylactic reactions.

2.2.2. Conclusions. The criteria are not fulfilled for including molluscs on a list of food allergens for labelling because there have been no DBPCFC.

3. Eggs and egg products

Reference to egg white as an allergen indicates hen's egg white, as this has been the focus of most research.

3.1. Double-blind, placebo-controlled food studies

Norgaard & Bindslev-Jensen (50) performed DBPCFC with whole fresh hen's egg in 13 adult patients with symptoms of food allergy. The challenge was positive in seven of them, and one patient reacted with severe exacerbation of asthma (40% decrease in FEV_1) within 15 min after ingestion of 50 mg of egg.

Lau et al. (51) performed an open oral challenge with lyophilized ovalbumin in children (from 3 months to 12 years of age) and reported that 10 mg elicited symptoms (not specified). However, all commercial sources of ovalbumin contain significant ovomucoid contamination, so that it is not certain whether the reaction was related, at least in part, to ovomucoid.

3.2. Anaphylactic reactions

Six children and adolescents who died of anaphylactic reactions to foods and seven others who nearly died and required intubation were identified (52). All had known food allergies, but had unknowingly ingested the foods responsible for the reactions. One was known to be allergic to eggs.

3.3. Antigenic composition

Egg white is more allergenic than egg yolk, but in some individuals, IgE can be found directed to egg-yolk proteins. Egg white contains 23 different glycoproteins. The major egg allergens appear to be ovomucoid (Gal d 1), ovalbumin (Gal d 2) (53), conalbumin (Gal d 3) (54–57), and lysozyme (Gal d 4).

Proteins cross-reacting with allergens in hen's egg white were studied in turkey, duck, goose, and seagull egg whites, in hen's egg yolk, and in hen and chicken sera and flesh (58). All egg whites contained proteins able to bind human IgE antibody in the sera of patients with allergy to hen's egg white. Several proteins cross-reacting with allergens in hen's egg white were also detected in egg yolk and in hen and chicken sera and flesh.

Cooked egg does not lose its allergenicity. Ovomucoid (53) and ovalbumin are heat-stable. However, DBPCFC studies using processed food containing hen's egg have not been reported.

3.4. Conclusions

1) DBPCFC studies have demonstrated that egg can cause allergic reactions.
2) Life-threatening reactions have been observed.
3) The amount of allergen required to induce allergic symptoms may be 10 mg or lower.
4) Cross-reactivities exist between hen, turkey, duck, goose, and seagull egg whites.
5) The allergens are heat-stable and therefore unlikely to be destroyed by processing.
6) The listing of eggs on a list of food allergens for labelling is appropriate.

4. Fish and fish products

Fish allergy has been known for many years (59). However, symptoms of food allergy should be distinguished from those induced by non-allergic reactions including histamine poisoning (60).

4.1. Double-blind, placebo-controlled studies using raw fish

Aas (61) used masked and capsule challenges of codfish in a group of 84 children ranging in age from 1 to 16 years. Twenty of these patients exhibited respiratory and skin symptoms to codfish ingestion.

Hansen & Bindslev-Jensen (62) studied 10 adults (21–31 years of age) with a medical history of immediate reactions after ingestion of minute amounts of codfish (two anaphylactic shocks). Seven of them had positive DBPCFC in which most of the reported symptoms proved to be reproducible. The amounts of fish inducing positive DBPCFC ranged from 6 mg for oropharyngeal symptoms to over 10 g for anaphylactic symptoms. In these patients, a skin prick test with the fresh fish was positive in 7/7 and the commercial RAST was positive in 6/7.

4.2. Anaphylactic reactions

Yunginger et al. (40) identified seven cases of food-related fatal anaphylaxis involving five males and two females, aged 11–43 years. One of them was allergic to fish. In this particular case, the patient died after eating potatoes fried in the same pan as fish. Thus, while the amount of fish was not quantified, it was probably quite low.

4.3. Antigens and cross-reactivities between fish species

Allergen M (Gad c 1) from codfish was the first extensively studied allergen. Codfish hypersensitivity is common in countries where there is a high consumption of this fish. Allergen M is a parvalbumin found in the muscle of fish and amphibians. It has a molecular weight of approximately 12 kDa, is heat-stable, is partially resistant to proteases, and exists as a single polypeptide chain (59, 63, 64). Linear peptides corresponding to amino-acid regions 13–32, 49–64, and 88–103 have been synthesized, and they bind IgE from cod-allergic subjects (65). A major allergen of salmon is a parvalbumin (Sal s 1) (66).

There appear to be some species differences, but extensive cross-reactivities exist among fish species (67–71).

4.4. Fish products

Cooking appears to reduce the allergenicity of fish, but not eliminate it, as indicated by immunochemical analysis including SDS–gel electrophoresis and ELISA inhibition (72). In a clinical study, 18 fish-allergic patients did not react when challenged with canned tuna, and neither of the two salmon-allergic patients reacted when challenged with canned salmon.

In another study, SDS–gel electrophoresis and immunoblot analyses showed that fish proteins were denatured by cooking and formed high-molecular-weight aggregates (63).

These findings suggest that at least some of the major allergens of fish responsible for IgE-mediated food allergy are more labile than previously recognized. However, fish-allergic patients should be warned that some fish allergens may be present in processed fish (for example, Surimi [73]) and could cause severe allergic reactions if ingested.

4.5. Conclusions

1) DBPCFC studies demonstrated that fish can cause allergic reactions.
2) Life-threatening reactions and even fatal reactions have been observed.
3) The amount of allergen required to induce allergic symptoms may be as low as 6 mg, as suggested by respiratory allergic reactions associated with airborne fish particles (74).
4) Cross-reactivities exist between different fish species.
5) Fish allergens are considered to be heat-stable, but studies have suggested that some of the major allergens responsible for IgE-mediated food allergy to fish are more labile than previously recognized.
6) Some food processing may cause reduction of allergenicity; e.g., canned salmon and tuna. There are no data on possible reactions to fish oil (however, see Section 10, Conclusions, for a general comment on edible oils).
7) The inclusion of fish on a list of food allergens for labelling is appropriate.

5. Peanut, soybean, and other legumes

Soybean and peanut are members of the legume family and share several common antigenic fractions with other legumes such as peas, lentils, and beans. Thus, patients allergic to one of these foods have serum IgE antibodies that immunologically cross-react with other legumes. Despite the common finding that peanut-allergic individuals have both positive skin prick tests and cross-reacting antibodies to proteins in other legumes, it is rare for this to be clinically relevant. However, a recent study showed that patients with severe peanut-allergic reactions may suffer from soybean anaphylaxis (75). Where clinical cross-reactions do occur, they tend to be mild with legumes other than soybean, but severe and occasionally life-threatening with peanut (76–80). Peanut allergy can cause life-threatening reactions (81).

5.1. Peanut

5.1.1. Double-blind, placebo-controlled studies. Over a 10-year period, 114 children aged 1–14 years were challenged because of a history of adverse reaction. Sixty-eight had negative challenges and were able to eat peanuts. Forty-six had positive challenges with symptoms ranging from minor cutaneous responses to gastrointestinal and respiratory symptoms (80). Other DBPCFC studies have confirmed the importance of peanut as a major food allergen (8, 20, 21). Most other studies have relied on clinical history and positive skin test and/or RAST, with only a small number having subsequent challenge.

5.1.2. Anaphylactic reactions. Peanut is a common cause of anaphylaxis in the UK and the USA (39, 81–84). Severe reactions have also been associated with abdominal pain at the onset of the response (85).

Four out of 13 food-allergic children and adolescents who died, or nearly died, from accidental ingestion of foods, reacted to peanuts contained in foods such as candy, cookies, and pastry (52). Yunginger et al. (40) identified seven cases of food-related fatal anaphylaxis involving five males and two females, aged 11–43 years. Four of these patients were allergic to peanut. The common features in those who died were known allergy, ingestion of food outside the home, a strong association with asthma, and a failure to use appropriate adrenaline rescue treatment.

5.1.3. Antigenic composition. Antigens and cross-reactivities to major peanut allergens have been characterized; the former are termed Ara h 1 and Ara h 2 (6, 7). Much progress has been made in characterizing IgE responses to recombinant peanut allergen (86). Thermal denaturation of peanut protein extracts does not enhance or reduce IgE- and IgG-specific binding activity (87). Chemical denaturation appears to reduce minimally the binding of these proteins (87). Ara h 1 is resistant to degradation under treatment with enzymes such as those of artificial gastric fluid (88).

Trace levels of peanuts can elicit adverse reactions, and a recent study has suggested that doses as low as 100 μg might initiate the first subjective symptoms (89). Cross-contamination of such amounts could easily occur, as for example, in oil used to cook peanuts (90). A polyclonal antibody assay specific to peanut proteins has been developed (91).

5.1.4. Processed food. Refined (neutralized, bleached, deodorized) peanut oil does not contain allergenic proteins. Cold-pressed peanut oils may contain peanut allergen (92). In a double-blind, crossover food challenge with crude peanut oil and refined peanut oil in 60 subjects allergic to peanuts, none reacted to refined oil, and six (10%) reacted to the crude oil (93).

Peanuts are used in a wide array of processed foods, and anaphylactic reactions to hidden peanut allergen have been reported (94, 95).

5.1.5. Conclusions

1) DBPCFC studies have demonstrated that peanut can cause allergic reactions.
2) Severe life-threatening reactions and some fatal reactions have been observed. In many countries, peanut is probably the food allergen most commonly inducing severe reactions.
3) The amount of allergen required to induce allergic symptoms may be as low as 0.1–1 mg.
4) Refined peanut oil should be distinguished from crude peanut oil. The use of other names of the oils, such as ground nut, should be eliminated.
5) Food processing does not appear to cause loss of allergenicity, with the exception of high-temperature refining of peanut oil.
6) The inclusion of peanuts on a list of food allergens for labelling is appropriate.

5.2. Soybean

Soybean was found to be a food allergen several decades ago. More recently, it has been identified as an occupational aeroallergen inducing asthma (96).

5.2.1. Double-blind, placebo-controlled studies. DBPCFC (77, 97, 98) have demonstrated that soybean may induce allergic reactions. Burks et al. studied eight children with atopic dermatitis who had developed skin reactions during DBPCFC (97). In another study of 30 patients with positive skin tests to soybean, 10 patients showed positive DBPCFC.

5.2.2. Anaphylactic reactions. Anaphylactic reactions have been reported in patients being tested with elimination diets for atopic eczema. Four out of 80 patients had anaphylactic reactions on reintroduction of a single food, one of which was to soybean (99).

Yunginger et al. (100) reported a case of fatal anaphylaxis to soybean. Sixty cases of severe allergic reactions caused by foodstuffs have been reported in Sweden since 1993 (75). Five of these reactions were fatal. Of all reactions, 18% were caused by soybeans. These reactions mainly occurred in children and adolescents with severe peanut allergy and asthma. In many cases, severe symptoms appeared more than 1 h after soybean intake. The report suggests that soybean allergy is underestimated as a risk factor for severe reactions.

5.2.3. Antigenic composition. Several antigens have been identified, including Gly m 1A and Gly m 1B, which have been identified as responsible for soybean-induced asthma. A major allergen has been identified, and substantially complete removal (99.8%) of the allergenic soybean protein, Gly m Bd 30 K, was attained by physical techniques (101, 102).

Thermal denaturation of soybean-protein extracts does not affect IgE- and IgG-specific binding activity (87). Chemical denaturation appears to reduce minimally the binding of these proteins (87).

5.2.4. Conclusions

1) DBPCFC studies have demonstrated that soybean can cause allergic reactions.
2) The amount of allergen required to induce allergic symptoms is unknown.

3) Cross-reactivities exist between peanut and soybean and may have some clinical relevance.
4) Soybean allergens are considered to be heat-stable.
5) Food processing may not cause loss of allergenicity.
6) The inclusion of soybeans on a list of food allergens for labelling is appropriate.

5.3. Other members of the legume family

Legumes are one of the world's important sources of food, especially in developing countries. However, besides peanut and soybean, other members of the legume family (e.g., pea, green bean, sweet lupine, and lentil) were rarely found to induce allergic reactions (95, 103, 104). Cross-reactivity among legumes may occur, but *in vitro* studies defining common allergenic determinants among these food substances cannot be automatically interpreted as reflecting *in vivo* cross-reactivity. Furthermore, limited attempts at DBPCFC in specific patients have not confirmed cross-reactivity in peanut-sensitive individuals to other legumes (76, 77).

Therefore, it does not seem necessary to include legumes other than peanut and soybean in the list of food allergens for labelling.

6. Milk and milk products

Cow's milk protein intolerance is relatively common in infancy. It occurs in about 2–5% of infants, but the prevalence decreases with age. Intolerance of cow's milk involves several mechanisms in which allergy is uncommon, as compared with lactose intolerance, for example. Intolerance of lactose is not mediated by the immune system and will not be considered in this document. Allergy to cow's milk is mainly an IgE-mediated allergic reaction, but other immune mechanisms are likely (105). Allergy to cow's milk may be acquired later in life. Allergic reactivity to cow's milk is lost during childhood in the vast majority of cases (106).

6.1. Double-blind, placebo-controlled studies

Cow's milk has been shown in many studies to elicit immediate or delayed allergic reactions, including anaphylactic shock and even fatal reactions, eczema, and wheezing (8, 20, 50, 107).

6.2. Anaphylactic reactions

Anaphylaxis (108), including fatal reactions, has been observed in milk allergy (52). Traces of milk as a hidden allergen may induce anaphylactic reactions (109, 110).

6.3. Antigens and cross-reactivity

IgE analysis and challenge tests show that most cow's milk-allergic patients react to several protein fractions of cow's milk including casein (Bos d 8), α-lactalbumin (Bos d 4), and β-lactoglobulin (Bos d 5) (111, 112), serum albumin (Bos d 6), and immunoglobulin (Bos d 7). However, casein was shown to produce the highest rate of skin test reactivity in children with milk allergy (113, 114), β-lactoglobulin produced the highest rate of positive oral challenges (115), and α-lactalbumin was occasionally positive in skin tests and oral challenge. Patients may react to one or more of several protein fractions of cow's milk, and the range of reactions differs from patient to patient.

Usually, there are cross-reactivities between goat's and cow's milk (116). However, there are reports of allergy to cheese produced from sheep's and goat's milk, but not to cheese produced from cow's milk (117).

6.4. Cow's milk-based hydrolysates intended for infant feeding

Since cow's milk allergy is most common in infants and young children, alternatives to ordinary cow's milk-based substitutes for human milk in infant feeding have been manufactured. Protein hydrolysates possess biologic and immunologic properties which depend largely on the extensiveness of enzyme hydrolysis and ultrafiltration (118, 119). Although the extensively hydrolyzed protein formulae are hypoallergenic and have demonstrated a high safety profile in cow's milk allergy, they are not completely nonallergenic, and allergic reactions have been triggered in some situations. Such formulae appear to be safe in nonsensitized infants even if given as part of an allergy-prevention programme (120–122). In contrast, partially hydrolyzed milk protein formulae are not intended for therapy in cow's milk allergy (119, 123, 124). The effectiveness of hydrolyzed cow's milk formulae in the prevention of allergic diseases remains uncertain, however, except for the reduction of cow's milk allergy in early childhood (121, 125).

Table 1. Major allergens from foods
Official list of food allergens, IUIS Allergen Nomenclature Subcommittee (San Francisco, 1997)

Allergen source	Systematic and original names	MW kDa
Apium graveolens (celery)	Api g 1	16
Brassica juncea (oriental mustard)	Bra j 1; 2S albumin	14
Hordeum vulgare (barley)	Hor v 1; BMAI-1	15
Malus domestica (apple)	Mal d 1	18
Oryza sativa (rice)	Ory s 1	18
Prunus avium (sweet cherry)	Pru a 1	2
Sinapis alba (yellow mustard)	Sin a 1, 2S albumin	14
Glycine max (soybean)	Gly m 1A; HPS	7.5
	Gly m1B; HPS	7
Arachis hypogaea (peanut)	Ara h 1; vicilin	63.5
	Ara h 2; conglutinin	17
Actinidia chinensis (kiwi)	Act c 1; cysteine protease	30
Gadus callarias (cod)	Gad c 1; allergen M	12
Salmo salar (Atlantic salmon)	Sal s 1; parvalbumin	12
Bos domesticus (domestic cattle) (milk)	Bos d 4; α-lactalbumin	14.2
	Bos d 5; β-lactoglobulin	18.3
	Bos d 6; serum albumin	67
	Bos d 7; immunoglobulin	160
	Bos d 8; caseins	20–30
Gallus domesticus (hen)	Gal d 1; ovomucoid	28
	Gal d 2; ovalbumin	44
	Gal d 3; conalbumin (Ag 22)	78
	Gal d 4; lysozyme	14
Metapenaeus ensis (shrimp)	Met e 1; tropomyosin	36
Penaeus aztecus (shrimp)	Pen a 1; tropomyosin	36
Penaeus indicus (shrimp)	Pen i 1; tropomyosin	34

6.5. Conclusions

1) Studies employing DBPCFC have demonstrated that cow's milk causes allergic reactions.
2) Life-threatening and even fatal reactions have been observed.
3) The amount of allergen required to induce allergic symptoms may be very low but is likely to be in the milligram range.
4) Cross-reactivities exist between milk from different species of mammals.
5) Milk allergens are heat-stable.
6) Food processing may cause loss of allergenicity.
7) Extensively hydrolyzed milk formulae are available that may be given to children with documented milk allergy after appropriate confirmation of safety in the individual child.
8) The inclusion of milk and milk products on a list of food allergens for labelling is appropriate.

Table 2. Shell (nut) fruits

Name	Latin name	Family/subfamily
Cashew nut	*Anacardium occidentale*	Anacardiaceae
Peanut	*Arachis hypogaea*	Fabaceae
Hazelnut	*Corylus avellana*	Betulaceae
Almond	*Prunus dulcis*	Rosaceae
Brazil nut	*Bertholletia excelsa*	Lecythidaceae
Pistachio	*Pistacia vera*	Anacardiaceae
Walnut	*Juglans regia*	Juglandaceae

7. Tree nuts and nut products

Tree nuts are shell (nut) fruits of various families (Table 2). Acute allergic reactions to a range of different nuts have been reported for many years. There is an important taxonomic distinction between tree nuts and peanuts (or groundnuts), which are legumes. The relevance of this distinction at the family taxonomic level is uncertain as phylogenetic links at higher levels (e.g., order) may also be important. A high percentage of peanut-allergic individuals are reported to have tree-nut allergies (81, 82). Tree nuts are among the most common foods to cause allergy in the Scandinavian countries (75, 126) due to cross-reactivities with birch pollen.

7.1. Double-blind, placebo-controlled studies

In order to extend previous investigations of adverse reactions to foods, 68 children, aged from 5 months to 15 years, were studied by DBPCFC (98). Sixteen out of 43 subjects, 3 years of age or older, had 22 adverse reactions during 94 food challenges with one or more of 14 foods. All confirmed reactions were to either peanut, tree nuts, milk, egg, or soybean.

Oral allergy syndrome is common in pollinosis patients after ingestion of nuts. Pistachio nut allergy was demonstrated with DBPCFC in one patient (127).

7.2. Anaphylactic reactions

Yunginger et al. (40) identified seven cases of food-related fatal anaphylaxis involving five males and two females, aged 11–43 years. One of the patients was allergic to pecan.

Another study identified six children and adolescents who died of anaphylactic reactions to foods and seven others requiring intubation who nearly died. Six were allergic to nuts (52).

Anaphylactic reactions have been reported to Brazil nut (128), cashew nut (129), pine nut (130, 131), pistachio nut (132), and walnut (75, 81).

7.3. Processed foods

A study was carried out to determine whether several of the new "gourmet" tree-nut oils (walnut, almond, hazelnut, pistachio, and macadamia) contain residual proteins that could bind IgE from sera of patients with allergy (133). IgE binding was assayed by slot-blot and Western immunoblotting. Extracts derived from oils that had undergone less processing at lower temperatures tended to demonstrate qualitatively greater IgE binding and higher protein concentrations. Tree-nut oils which are not fully refined may pose a threat to nut-allergic individuals.

Anaphylactic reaction caused by neoallergens (newly formed during the heating process) in heated pecan nut was observed in an atopic girl who had eaten cookies containing pecan nuts (134). Investigations revealed that she had developed IgE antibodies specific against the allergenic determinants present in aged or heated pecan nuts, but not in fresh pecan nuts. Neoallergens appearing during heating or storing of foods may be important in some anaphylactic reactions.

7.4. Antigens and cross-reactivities

Patients allergic to birch and other Betulaceae pollen (135) or latex (136) have cross-reacting antigens with various nuts; however, nut allergy may also be observed in patients without such cross-reactivities. Reactions to hazelnut are therefore common in areas where birch and other Betulaceae species pollinate. Identification of common allergenic structures in hazel pollen and hazelnut offers a possible explanation of sensitivity to hazelnut in patients allergic to tree pollen (137).

Brazil-nut protein was identified as an allergen in soybeans that had been genetically modified to contain the Brazil nut 2S albumin protein as a source of methionine (138). This example provides a demonstration of the efficacy of the allergenicity-assessment strategy that has been devised for genetically modified foods. As a consequence of this finding, the company responsible decided not to market the transgenic soybean.

7.5. Conclusions

1) DBPCFC studies demonstrated that tree nuts can cause allergic reactions.
2) Life-threatening reactions and even fatal reactions have been observed. In the Scandinavian countries, hazelnut is probably the most common food allergen inducing severe reactions.
3) The amount of allergen required to induce allergic symptoms may be very low but has to be defined.
4) Cross-reactivities exist between different species.
5) Food processing may alter allergenicity.
6) The inclusion of tree nuts on a list of food allergens for labelling is appropriate.

8. Seeds

8.1. Double-blind, placebo-controlled studies and anaphylactic reactions

Information on seed allergies is scant. However, there are case reports of anaphylactic reactions to sunflower seed (139, 140), millet (141), sesame seed (142–144), cottonseed (145–147), and mustard seed (148, 149). Sesame seed appears to be an increasingly common cause of food allergy inducing severe anaphylactic reactions (150). It was found to induce anaphylaxis even as a hidden allergen (151). Moreover, anaphylaxis to sesame oil has also been reported (152, 153). Anecdotal reports suggest that sesame seed is an increasing cause of food-induced allergy in the USA and the UK because of its extensive use in bakeries. Furthermore, annatto, a common orange/yellow food colouring, extracted from the seeds of a tree (*Bixa orellana*), has been reported to cause anaphylaxis (154).

Sesame seed was found to induce allergic symptoms in a DBPCFC (150).

8.2. Antigens and cross-reactivities

Allergy to poppy seed and/or sesame seed often occurs in patients with simultaneous sensitization to nuts and flour. Common allergenic structures in hazelnut, rye grain, sesame seed, and poppy seed have been identified (155).

Some seed allergens have been identified. Yellow mustard seed has been studied in rather more detail in relation to major allergenic components. The major allergen Sin a 1 is fully characterized (156–158).

8.3. Conclusions

1) Anecdotal reports supported by skin test, IgE antibody testing, and occasional DBPCFC studies suggest an increasing acceptance that certain seeds cause food allergy in sensitive individuals.
2) Life-threatening reactions have been observed.
3) The amount of allergen required to induce allergic symptoms may be very low but has to be defined.
4) Unrefined sesame seed oil contains allergens.
5) The inclusion of sesame seed on a list of food allergens for labelling is appropriate. However, more data are needed before deciding whether other seeds should be included.

9. Other foods

9.1. Prunoideae subfamily (peach, plum, apricot, cherry, almond)

The principal fruits of the Prunoideae subfamily are almond, peach, plum, apricot, and cherry. The latter are all stone fruits, whereas almond is a shell (nut) fruit (38) (Table 2). The allergy to foods of this subfamily has not been extensively investigated, and only open challenge studies have been carried out (159). In 112 patients with a history suggestive of food allergy beginning after the age of 10 years, 49 challenges were positive for peach (75%) and 28 were positive for almond (39%) (160).

Anaphylactic reactions have been observed with cherry, peach, and almond (83, 161–163). An anaphylactic reaction to several members of the Prunoideae subfamily was observed in a latex-allergic patient (164).

Cross-reactivity between peach, plum, apricot, and cherry has been studied using open challenge in 19 patients allergic to peach (165). Five of 19 patients also had positive challenge with three other Prunoideae fruits (cherry, plum, or apricot). This study reported the presence of a 13-kDa major allergen, identified by SDS–PAGE immunoblotting, which was remarkably homologous in all the Prunoideae fruits. Two other major allergens were identified: a 14-kDa allergen in peach and a 30-kDa allergen in cherry.

However, the extent to which food processing may cause a marked reduction in Prunoideae allergens has to be determined, although many patients allergic to fruits can tolerate them when they are cooked.

9.1.1. Conclusions. The evidence for including foods from the Prunoideae subfamily in a list of food allergens for labelling is still insufficient because the criteria have not been fulfilled. Separating almonds from tree nuts (on taxonomic grounds) and applying the strict criteria resulted in this nut type not requiring labelling. This conclusion may not be appropriate and reflects the difficulty of applying strict criteria (see section 10, Conclusions).

9.2. Celery

There have been reports of immediate symptoms upon contact with celery root in subjects with positive skin test to this vegetable. Several anaphylactic reactions to celery have been reported (166–170). Unfortunately, there are no reports of either single-blind challenges or DBPCFC.

Cross-reactivities between celery and other foods (especially of the Umbelliferae family) and pollen have also been described; for example, celery–carrot–mugwort pollen–spice syndrome and celery–birch associations (171, 172). However, no studies have confirmed celery allergy with DBPCFC. The major allergen of celery, a 16-kDa, Bet v 1-related protein that has been identified by recombinant techniques as a 153-amino-acid (16.2 kDa) protein, has been named Api g 1 (173). A second major celery allergen is profilin, which may be more rarely associated with symptoms (174, 175).

There are insufficient data on the stability of celery in processed foods. However, Api g 1 appears to be thermostable; Api g 2 is more thermolabile (176).

9.2.1. Conclusions

Celery does not fulfil the criteria for inclusion on a list of food allergens for labelling because there have been no DBPCFC.

9.3. Rice

Food allergy to rice appears to be rare in Western countries (177) but seems to be more common in Asia (178, 179). Unfortunately, none of the studies on rice allergy have been confirmed by DBPCFC. One anaphylactic reaction to rice has been diagnosed by single-blind challenge with rice (180).

The major allergen of rice is a 16-kDa protein tentatively designated RP16kD (181), but there are two other major allergens: a 15.5-kDa protein (97% positivity) and a 19-kDa protein (56% positivity), as well as an intermediate allergen of 90 kDa (44% positivity) (182). However, the two relevant studies (181, 182) do not report how patients were selected; in particular, there is no indication of whether or not rice challenges were performed in the selection process. The lack of such data can confound the interpretation of the results, inasmuch as high levels of cross-reactivity are known to exist, as confirmed by RAST inhibition between RP16kD and other cereals (wheat, corn, Japanese millet, and millet). Moreover, there seems to be some similarity between the IgE binding of rice-grain proteins (16, 26, and 32 kDa) and proteins of rice pollen (179). The high frequency of allergenic cross-reactivity and the lack of accurate patient-selection procedures, i.e., they are not based on DBPCFC, calls for caution in the interpretation of study results.

Matsuda has cloned the cDNA of the 16-kDa protein and has also worked out its amino-acid sequence. The 16-kDa protein appears to be very similar to the amylase/trypsin inhibitor of wheat and barley (183). Reduction of the 14–16-kDa allergenic proteins was obtained in transgenic rice plants by antisense gene strategy to produce hypoallergenic rice (184).

Rice with reduced allergenicity has also been obtained by enzymatic treatment, and such rice may improve rice-associated atopic dermatitis (185, 186). With antibodies raised against major food allergens, it is possible to screen for plant strains containing low amounts of a major allergen, as in the case of the 16-kDa rice allergen (187), making it possible to select "low-allergenic" strains. However, at present, an assessment of the efficacy of hypoallergenic rice is not available, especially in regard to the clinical expression of IgE-mediated symptoms. Although some Eastern countries now market hypoallergenic rice, the efficacy of these products in reducing allergic symptoms in rice-allergic subjects has not been confirmed. Moreover, biotin deficiency has been observed in an infant fed amino-acid formula and hypoallergenic rice (188).

9.3.1. Conclusions. The criteria have not been fulfilled to include rice on a list of food allergens for labelling, although one DBPCFC has been reported.

9.4. Buckwheat

So far, there are no reports of DBPCFC with buckwheat. Several case reports document symptoms suggesting allergy to buckwheat: urticaria, asthma, and even anaphylaxis (189, 190). Skin prick tests were positive; allergen-specific IgE antibodies were present. This suggests an IgE-mediated reaction mechanism. No data on the threshold for oral challenge are available.

Cross reactivity with latex has been reported (191).

9.4.1. Conclusions. Buckwheat does not fulfil the criteria for inclusion in a list of food allergens for labelling because there have been no DBPCFC.

10. Conclusions

Food-allergic reactions can be unpleasant, resulting in reactions such as tingling of the lips and mouth or gastrointestinal upset. Of greatest concern are those individuals who are highly sensitive to particular foods consumption of which can lead to life-threatening reactions.

Although it might be desirable to label all ingredients of food, this is not feasible. Therefore, decisions have to be made as to which food ingredients are important allergens and must always be labelled.

The purpose of this review was to establish scientific criteria for deciding whether a foodstuff is commonly allergenic in sensitive individuals.

The criteria for placing a food on a list of allergenic foods were as follows:

1) report of a properly conducted DBPCFC study confirming allergenicity
2) reports of assessment of the severity of the reaction in foodstuffs causing severe systemic and life-threatening reactions should be listed.

In addition, there is a subset of criteria for evaluation of the quality of information in publications reporting food allergy.

The FAO consultation (1995) on food allergies confirmed a list of foods considered to be the most commonly allergenic. This provided the starting point for evaluation of foods by the criteria established. Certain foodstuffs known to cause allergenic reactions but not currently on the FAO list were also evaluated by the criteria.

For some foods, the scientific evidence for labelling has been obtained, but more data are needed in some cases.

The results of the evaluation are summarized in Table 3.

The criteria developed for evaluation of allergenic foods constitute a first step toward establish-

Table 3. Classification of food allergens

Foodstuff	DBPCFC documented	Fatal reaction	Anaphylactic reaction (IV)	Inclusion in list
Wheat*	Yes	No	Yes	Yes
Other cereals	Yes	No	No	No
Crustaceans	Yes	Yes	Yes	Yes
Molluscs	No	No	Yes	No
Eggs	Yes	No	Yes	Yes
Fish	Yes	Yes	Yes	Yes
Peanut	Yes	Yes	Yes	Yes
Soybean	Yes	No	Yes	Yes
Other legumes	Unclear**	No	Yes	No
Milk	Yes	Yes	Yes	Yes
Tree nuts***	Yes	Yes	Yes	Yes
Sesame seed	Yes	No	Yes	Yes
Other seeds	No	No	Yes	No
Prunoideae****	No	No	Yes	No
Celery	No	No	Yes	No
Rice	No	No	No	No
Buckwheat	No	No	Yes	No

*See section 1 on cereals containing gluten.
**Not sufficiently documented.
***See Table 2.
****Almonds are included in "tree nuts".

ing a scientific and objective method to determine a list of foodstuffs for labelling. Although scientific criteria help to ensure clarity and consistency in deciding which foods must be labelled, overrigid application of the criteria could lead to an inclusion or exclusion of certain foods which may be considered inappropriate in the light of clinical experience.

The amount of a specific protein necessary to elicit an allergic reaction cannot be calculated from presently available data with any degree of certainty for all individuals. This is because the tolerance of a particular food varies from one food to another and from one individual to another. It is important to distinguish between the amount of a particular food that will elicit a reaction and the amount of the specific protein in the food that will cause a reaction. However, some indications of threshold doses for certain allergenic foods can be obtained from careful clinical histories of reactions to particular amounts of food ingested and from doses of food used in DBPCFC studies.

Reports on the effects of food processing indicate that certain processes for certain foods can either eliminate, reduce, or not change the allergenic potential. Scientific data support the conclusion that ingestion of neutralized, bleached, and deodorized peanut oil does not trigger allergic reactions in peanut-sensitive individuals. Similar studies have not been carried out for all other types of edible oil; however, it may be reasonable to assume that full refining would remove protein from these oils to eliminate allergic potential in the same way as for peanut oil.

The results of further research are required to improve the scientific basis of the criteria outlined in this paper. This is also the case for further elucidation of the dose thresholds for foods below which allergenic reactions do not occur in sensitive individuals, and to understand the mechanisms whereby food processing can modify allergenic potential.

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