Threshold dose distributions for 5 major allergenic foods in children

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Background: For most allergenic foods, insufficient threshold dose information within the population restricts the advice on levels of unintended allergenic foods which should trigger precautionary labeling on prepackaged foods.
Objective: We wanted to derive threshold dose distributions for major allergenic foods and to elaborate the protein doses at which a proportion of the allergic population is likely to respond.
Methods: For 7 allergenic foods double-blind, placebo-controlled food challenges (DBPCFCs) with a positive outcome for allergic reactions were selected from the clinical database of children routinely tested to diagnose food allergy at the University Medical Center Groningen. For each allergen 2 population threshold distributions were determined with the individual minimal eliciting dose and the preceding dose of each DBPCFC for objective symptoms and any symptom (either subjective or objective).
Results: Individual positive DBPCFCs were available for peanut (n = 135), cow's milk (n = 93), hen's egg (n = 53), hazelnut (n = 28), and cashew nut (n = 31). Fewer children were challenged with soy (n = 10) or walnut (n = 13). Threshold dose distributions showed a good statistical and visual fit. The protein dose at which 5% of the allergic population is likely to respond with objective reactions was 1.6 mg for peanut, 1.1 mg for cow's milk, 1.5 mg for hen's egg, 7.4 mg for cashew nut, and 0.29 mg for hazelnut. Thresholds for any symptom were on average 2 to 6 times lower than for objective symptoms. The 95% upper and lower confidence intervals of the threshold distributions were overlapping. The peanut threshold distribution on objective symptoms was similar to the distribution of another European center.
Conclusions: Threshold distribution curves and eliciting doses are a powerful tool to compare different allergenic foods and for informing policy on precautionary labeling. (J Allergy Clin Immunol 2013;131:172-9.)

Key words: *Allergenic foods, threshold dose distributions, children, eliciting dose*

The only option for persons with food allergies to manage their food allergy is the strict avoidance of allergenic food. An increasing number of studies are being published on oral tolerance protocols for peanut, milk, egg, and wheat, although these procedures have not yet become standard practice. Most of the population with food allergy thus still relies on rigorous elimination of culprit allergenic foods from their diet. Legislation in many regions of the world, for instance, the European Union laid down in European Union directives 2003/89/EC and 2006/42/EC, prescribe the labeling of food products for several major allergenic foods or products derived from that allergen when added as ingredients to food. In addition, many food producers have incorporated allergen-auditing programs and voluntarily warn the allergic consumer to the potential presence of allergens by using precautionary labeling of food products, for example, "may contain xxx." However, despite this, recent studies show that a precautionary warning on products is not always valuable to allergic consumers. Surveys of commercially available products show that the presence or absence of a precautionary warning corresponds poorly with the actual presence of the allergen in the product,[1,2] which can lead to potentially dangerous situations.[3,4] A recent study in Canada showed that approximately 17% of persons with food allergies experiencing an accidental exposure attributed this to products with unintentional cross-contamination during manufacturing and no precautionary statement on the label.[4] Conversely, many products do not contain the allergen to which the precautionary warning on the label refers. As a consequence, consumers increasingly seem to ignore precautionary labels.[5] To improve this situation, quantitative guidance is needed with advice on levels of unintended allergens (also called action levels) to reduce the number of foods having precautionary labeling. Several initiatives have been created by both food industry and enforcement bodies with the involvement of various stakeholders to improve allergen management and to introduce more uniform and transparent risk information.[6-10] One of the ultimate goals may be to establish internationally harmonized guidance that includes action levels for labeling unintended allergens.

Previously, a probabilistic risk assessment method for use in population risk assessment has been developed and successfully applied.[1,3,6,11] The risk assessment method quantifies the number of allergic responders that can be expected when a particular product contains a specified amount of a certain allergen, because it

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Abbreviations used
DBPCFC: Double-blind, placebo-controlled food challenge
ED: Eliciting dose
LOAEL: Lowest observed adverse effect level
NOAEL: No observed adverse effect level

combines the consumption patterns of foods in a defined population with the sensitivity of a population for an allergen.[1]

The population of young adults may be especially vulnerable, because they represent most of the fatalities in most registries for food-induced anaphylaxis.[12,13] A large proportion of children allergic to milk, soy, and egg are known to outgrow their allergy.[14-16] In contrast, adults with hazelnut allergy seem to respond with more severe reactions than children.[17] In addition, most adults allergic to cow's milk acquired the allergy at adult age, and reported symptoms which were more severe than symptoms seen in children.[16,18] Recently, it was shown in a cross-sectional study in a pediatric population that the eliciting dose of peanut (determined by the first symptom occurring during the double-blind, placebo-controlled food challenge [DBPCFC], either subjective or objective) may decrease with increasing age (up to 18 years).[19] However, it is largely unknown whether and to what extent threshold dose distributions are influenced by age. Because several aspects of food allergy seem to vary with age, it can be reasoned that there will be an effect on the eliciting dose (ED) as well. To address these issues and to make more threshold information for the pediatric population available to the community, including the food industry, we performed a structured retrospective study to retrieve data on individual minimal EDs for allergic reactions to several major allergenic foods in the pediatric outpatient population of the University Medical Center Groningen, The Netherlands, which were performed as a routine clinical procedure for the diagnosis of food allergy. These data were used to derive threshold distributions that were used to elaborate ED values.

METHODS

Study population and database review

The study population consisted of children in whom DBPCFCs with cow's milk, soy, hen's egg, peanut, hazelnut, walnut, or cashew nut were performed at University Medical Center Groningen between July 2001 and December 2009. Children were referred from primary and secondary care centers because of suspected food allergy. The only exclusion criterion was refusal by parents or the child to undergo the test, which was the case in >2% of patients. Specifically, history of severe reactions was not an exclusion criterion for DBPCFCs. Information on sex, age, the suspected food, baseline symptoms, allergen-specific IgE and/or a positive skin prick test, and allergic symptoms occurring after positive challenge sessions were obtained by retrospective review of the electronic database. This study was exempt from medical ethical approval, because DBPCFCs in children were performed as a routine diagnostic test. All parents consented with the performance of DBPCFCs.

DBPCFCs

DBPCFCs were performed as previously described.[20] Clinical symptoms and overall condition had to be stable, and children were instructed to discontinue antihistamines 72 hours before DBPCFC if possible. Before the DBPCFC, the food in question was avoided by the child for at least 6 weeks. Placebo and active challenges were administered in a random order on separate days with at least 2 weeks' interval in between. Randomization was determined by computer. Recipes for the test foods were prepared for each challenge session individually. For all foods (except walnut) validation of adequate blinding of the test materials was achieved by sensory testing in a dedicated food laboratory.[20,21]

Incremental scale

The allergenic food was administered in a 4- to 6-step incremental design in which progressively greater quantities of the same allergenic food were administered.[22] Pasteurized cow's or ultrapasteurized soy milk, cooked egg, roasted peanuts, roasted cashew nuts, unroasted hazelnuts, or roasted walnuts were used. The incremental scale and total challenge dose used are shown in Table I. The incremental scale was achieved by varying the volume of the test food. Time interval between 2 challenge doses was 30 minutes in almost all cases.

Documentation of symptoms and assessment of challenge outcome

Symptoms were classified as subjective or objective, and immediate (ie, within <2 hours if after the last challenge dose) or late onset (2 to 48 hours after the last challenge dose).[22] Challenge sessions in which children consumed <75% of the intended challenge dose in absence of symptoms were considered invalid. The challenge was discontinued when objective allergic symptoms occurred or when subjective allergic symptoms occurred twice on 2 successive administrations of the challenge material.

Subjective symptoms that were noted were itching of the oral cavity, itching of pharynx, abdominal pain, nausea, dizziness, or generalized pruritus. Objective reactions included urticaria, diarrhea, dyspnea, vomiting, lip swelling, rhinoconjunctivitis, and bronchoconstriction. A decrease in peak flow, decrease in heart rate, or anaphylactic shock was not reported. Challenge sessions and total challenge outcome were assessed according to the criteria as previously described.[22]

Threshold distributions

DBPCFCs with a positive outcome (allergy confirmed) were analyzed to identify individual lowest observed adverse effect levels (LOAELs) and no observed adverse effect levels (NOAELs), that is, the threshold dose for an allergic reaction (the minimum eliciting dose in an individual) and the preceding dose, respectively, for both *objective* and *any* symptoms. The latter reflects the first reaction to a dose observed, irrespective of the type of reaction. The allergic reactions in the DBPCFC were classified as subjective and/or objective. If a subject reacted while consuming a dose, the LOAEL was set at the dose actually consumed. In patients for whom repeated DBPCFC procedures with the same food were reported in the database, only the results of the first diagnostic session were used for analysis.

For each allergen a population threshold distribution was determined with LOAELs and NOAELs expressed as discrete doses in milligram of total protein of the allergenic food. For each subject, the true threshold lies, by definition, between the NOAEL and LOAEL doses.

Individual thresholds were therefore analyzed with the interval-censoring survival analysis approach as described by Taylor et al.[23] Persons reacting to the first challenge dose were treated as left censored, whereas persons failing to respond to the uppermost challenge dose were treated as right censored. In cases when the challenge was stopped because subjective symptoms occurred on 2 successive administrations, the NOAEL for objective symptoms was set at the last consumed dose and the LOAEL was right censored. Similarly, this approach was done for any symptom; thus, only left censoring takes place here for situations in which the subject immediately responded to the first challenge dose. For each allergen a number of left- and right-censoring cases occurred (see Table II). Data sets were considered of higher quality if more individual data points were interval censored.

The NOAEL and LOAEL data for objective symptoms or any symptoms were fitted into the threshold probability distribution models for each allergen separately. Data analyses and modeling were performed in SAS v9.1 (SAS Research Institute, Cary, NC) with the use of the LIFEREG as previously