

How much is too much?: Threshold dose distributions for 5 food allergens

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Background: Precautionary labeling is used to warn consumers of the presence of unintended allergens, but the lack of agreed allergen thresholds can result in confusion and risk taking by patients with food allergy. The lack of data on threshold doses below which subjects are unlikely to react is preventing the development of evidence-based allergen management strategies that are understood by clinician and patient alike.

Objective: We sought to define threshold dose distributions for 5 major allergenic foods in the European population.

Methods: Patients with food allergy were drawn from the EuroPrevall birth cohort, community surveys, and outpatient clinic studies and invited to undergo a food challenge. Low-dose, double-blind, placebo-controlled food challenges were undertaken with commercially available food ingredients (peanut, hazelnut, celery, fish, and shrimp) blinded into common matrices. Dose distributions were modeled by using

interval-censoring survival analysis with 3 parametric approaches.

Results: Of the 5 foods used for challenge, 4 produced similar dose distributions, with estimated doses eliciting reactions in 10% of the allergic population (ED₁₀), ranging from 1.6 to 10.1 mg of protein for hazelnut, peanut, and celery with overlapping 95% CIs. ED₁₀ values for fish were somewhat higher (27.3 mg of protein), although the CIs were wide and overlapping between fish and plant foods. Shrimp provided radically different dose distributions, with an ED₁₀ value of 2.5 g of protein.

Conclusion: This evidence base will contribute to the development of reference doses and action levels for allergens in foods below which only the most sensitive subjects might react. (J Allergy Clin Immunol 2014;■■■■:■■■■-■■■■.)

Key words: Food, allergy, threshold, peanut, hazelnut, celeriac, fish, shrimp, EuroPrevall

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The prevalence of allergic disease, including IgE-mediated food allergy, has increased in recent decades, and it is now estimated to affect up to 5% to 7% of infants and 1% to 2% of adults. Food allergies in infancy are dominated by cow's milk and hen's egg but are largely outgrown by school age.¹ However, allergy to peanut persists into adulthood, and is the dominant allergy in the United Kingdom,² France,³ North America,⁴ and Australia.⁵ In adulthood patterns of food allergies change, with new allergies emerging to foods such as crustacean and molluscan shellfish and fresh plant foods associated with sensitization to pollen. The lack of a definitive cure means patients with food allergy have to practice lifelong stringent avoidance of the foods to which they react. Furthermore, those at risk of severe reactions must carry rescue medication in case of accidental consumption of their problem food. Despite such management strategies, accidental ingestion of offending foods remains a major cause of severe allergic reactions,⁶ with manufactured and restaurant foods being largely responsible for causing fatal reactions.⁷ Food avoidance also imposes a significant burden on allergic consumers and their families and communities, impairing quality of life.⁸ Legislation is in place around the world that requires allergenic ingredients to be declared when used in prepackaged foods, irrespective of their level of inclusion.⁹ However, managing food allergens to avoid their presence in products in which they are not part of a recipe remains an issue. This can be challenging because exposure to tiny amounts of allergenic ingredients can trigger a reaction in some subjects, with a kiss from someone who has been eating a problem food being sufficient to trigger a reaction.¹⁰

Precautionary labeling to warn allergic consumers of the risk posed by such cross-contact allergens has become widespread. However, such warnings have increasingly lost their effectiveness because they are applied in an inconsistent manner and are not always reflective of either the likelihood of allergen

Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
 ED₁₀: Estimated dose eliciting a reaction in 10% of a study population
 OAS: Oral allergy syndrome

contamination¹¹ or a clinical reaction. As a result, consumers with food allergy are confused about ingredients contained in commercial food products.¹² They consider information to be unclear or insufficient, leading to personal stress and feelings of insecurity¹³ and potential risk taking. In addition, there is confusion about interpretation of precautionary labels among health professionals who provide allergic consumers with advice on how to manage their condition.

Data are required as to what levels of allergen contamination can be considered to pose a small risk for most consumers with food allergy to develop more meaningful allergen labeling and management strategies. Regulatory authorities and others have taken the view that although threshold doses for allergens exist below which reactions do not occur, such thresholds have yet to be defined.^{14,15} Such information has been gained from human subjects with food allergies by using low-dose oral food challenges to define the question of "how much is too much."¹⁶ A wealth of data have been collected for peanut, which has allowed modeling of dose distribution, an approach that is now well accepted,^{15,17-20} forming a sound basis for assessing the risk posed by small amounts of this most notorious allergenic food.²¹ A major aim of the EuroPrevall project²² was to gather threshold data in the European population through studies undertaken in a pan-European birth cohort²³ together with community and related outpatient clinic studies.²⁴ Food allergy

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