

How Much Food Is Too Much? Threshold Doses for Allergenic Foods

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This review summarizes recent findings and controversies in the area of threshold doses for allergenic foods. Over the years, there have been many clinical reports that ingestion of small amounts of food can elicit IgE-mediated allergic reactions. In exquisitely allergic individuals, the threshold dose for elicitation of such reactions is often considered to be zero. However, some food-allergic patients report that they can tolerate small quantities of allergenic food. Are very low quantities hazardous to food-allergic consumers? How much of the offending food is too much? Why is the concept of a threshold level important? There have been very few studies to date on threshold doses for allergenic foods, and more research is needed in this important area.

Introduction

It is estimated that there are 29,000 emergency room visits and approximately 150 deaths in the United States each year due to anaphylactic reactions to foods [1••]. Individuals with food allergies often react adversely to the ingestion of very low amounts of unexpected sources of allergenic foods, including trace residues of the offending food that contaminate other foods. Trace contamination may arise from practices in the food industry, restaurants, and in homes and schools. Food service employees and food processors alike must be very cautious about the use of shared utensils and equipment. Most of the deaths from inadvertent exposure to allergenic foods among sensitive individuals have occurred in food service situations (restaurants, schools, homes). Lack of labeling and lack of knowledge of food components among both wait/kitchen staff and food-allergic customers appear to be key contributing factors in cases of severe reactions to foods in food service situations.

Creative recipe formulation as a by-product of increased demand among the population for variety in the foods we eat and the ever-increasing consumption of food

prepared outside the home may assist in producing reactions to hidden food allergens. While most of these reactions occur after ingestion of a food that is prepared in a food service environment, rather than to a packaged food product, the food processing industry has been subject to increasing scrutiny of allergen control in their processing plants. Because of various limitations and practices in food processing, foods may occasionally contain trace residues of the other food that may not be declared on the ingredient label.

The food industry began investing a significant amount of time, money, and effort to attain better allergen control in manufacturing facilities [2] several years ago, after publication of two key papers describing deaths and near-deaths from inadvertent ingestion of allergenic foods [3,4]. A more recent study outlined 32 cases of anaphylactic deaths due to inadvertent ingestion of allergenic foods; the authors made an ardent plea for more stringent food labeling requirements and increased education of the food-allergic individual with respect to labeling terms and how to avoid allergenic foods [1••]. In the last five years, commercialized test kits for detection of some allergenic foods have allowed food manufacturers to test their equipment and products for undeclared residues, and regulatory agencies have used the kits to investigate complaints from food-allergic consumers. However, regulatory and risk assessment decisions are missing important data in the form of threshold doses at the current time.

In addition to the food industry, the medical community and patients could benefit from increased information regarding threshold doses. Questions arise for allergists, nurses, and dietitians regarding purchasing behavior, modifications, and cautions for food-allergic individuals. Food-allergic patients often have questions about how much of their offending food they can tolerate, and whether ingredients like soy lecithin, wheat starch, and refined peanut and soy oils, which all contain very low levels of protein, are safe for them to eat. Many pediatric allergists do not recommend that their soy-allergic patients avoid soy lecithin, for example, and it is known that there are IgE-binding proteins present in low levels in soy lecithin. These types of questions are more adequately answered with some knowledge of threshold doses below which reactions are unlikely to occur.

Double-Blind, Placebo-Controlled Food Challenge Data

At present, very little information exists on which to estimate the threshold dose for specific allergenic foods. Anecdotal reports indicate that reactions have occurred from such incidental contact as opening packages of the offending food, wiping counters or tables containing unseen peanut residues, inhaling vapors from cooking of the food, use of shared utensils, and kissing someone who has eaten the offending food. Although such reports confirm that ingestion of very small amounts of allergenic foods may provoke allergic reactions in some exquisitely sensitive individuals, they do not provide quantitative information about lowest provoking doses. The gold standard for diagnosis in food allergy is the double-blind, placebo-controlled food challenge (DBPCFC). While this method has been used over the years for diagnosis and also in research involving comparison of DBPCFC with *in vitro* methods, some information on doses that elicit reactions may be gleaned from this data.

The concept in most cases, of course, was not to evoke a response to a threshold dose, but to make a diagnosis. In addition, false negative challenge results may be dangerous. Therefore, many of these studies reported use of, and reactions to, fairly large doses of allergen, in the range of several to many grams. While data from studies that began with large dose levels are useful in finding a starting point for looking at thresholds, one must begin looking at studies in which doses were started at lower levels to begin to get a picture of the possible threshold ranges for allergenic foods.

Another question involves whether patients selected for DBPCFCs are representative of the entire population of individuals with allergies to that specific food. Most allergists indicate that they exclude some or all of their most exquisitely allergic patients from challenge studies, but some are adamant that they challenge all of their patients. There are certain other factors that likely may influence threshold doses. Other medical conditions, such as asthma and cardiovascular disease; concomitant exposure to other allergens, such as inhalants; and use of alcohol, may influence how much protein it takes to trigger a reaction [5••]. To date, these factors have not been studied in depth in relation to effects on evoking an allergic reaction.

Threshold Studies

A few studies designed specifically to determine threshold doses have been published, although one must look carefully for this data. The most recent threshold study reported in a full publication was on peanut and was done by Jonathan Hourihane and his team in the United Kingdom in conjunction with our research group at the University of Nebraska [6]. The subjects all had convincing histories of peanut allergy, and all had experienced

reactions during open challenges during a previous study. The past positive challenges were recorded to labial challenge with peanut or unrefined peanut oil (which characteristically contains low doses of protein). Twelve patients were included in the study, and doses were begun at 10 mg and ended at 50 mg. While subjective symptoms were noted at 100 mg with the most sensitive patient, objective symptoms were not noted until 2 mg, and four of the patients did not react to the highest dose of 50 mg.

Rance *et al.* [7] reported a study commencing with low doses of peanut in which a total of 125 peanut-allergic individuals were challenged with a range of 1 mg up to 5 g. Six subjects (4.8%) reacted to the 1-mg dose, and 45 (36.2%) reacted to a cumulative dose below 100 mg. One of the first studies to use low levels of allergenic food was done by Hansen and Bindslev-Jensen [8], who found that the minimum dose of codfish needed to elicit a reaction (starting at 5 mg and going up to 5 g) was 6 mg. In conjunction with Dr. Wesley Burks of Arkansas Children's Hospital and Drs. Scott Sicherer and Hugh Sampson of Mt. Sinai Medical Center, we are currently performing a threshold study on egg in which the lowest dose eliciting objective reactions to date (seven positives out of 27 challenges) in egg-allergic children is 3.33 mg [9]. The reactions were all successfully treated with antihistamine alone. In addition, several parents have discovered that their children are no longer allergic to egg because of participation in this study.

Considerations and Confounding Factors

The threshold dose might best be defined as the lowest amount of the offending food that would elicit mild, objective symptoms (*eg*, mild urticaria, oral allergy syndrome) in the most sensitive individuals. We have moved away from the concept of challenging with food in capsules. Instead, we prefer the use of food vehicles, which mimics more closely real life experiences and lets the physician observe reactions initiated in the oral cavity, thereby stopping challenges at an earlier stage before more severe symptoms begin. The amount of the offending food needed to elicit symptoms is variable, possibly over an order of magnitude or more among different individuals with the same type of food allergy. Also, the threshold doses for different allergenic foods, *eg*, peanuts and eggs, might not necessarily be equal. While peanut allergy has garnered a lot of attention because of the significant proportion of deaths caused by peanut that have been recorded in the literature, some physicians deplore the almost singular attention paid to peanut and tree nut allergy, as some of the most severe reactions to challenges they have seen have been due to other allergenic foods [5••].

Consumer Complaint Samples

One way to estimate the lowest provoking dose of food is from actual samples from allergic consumer complaints.

Careful histories have to be taken from these individuals, as the perception that one has a food allergy is quite high among the general population while the true prevalence in the United States is estimated at 2% to 2.5% [10]. Comparatively few such estimates have been made involving a rather small number of individuals. This likely is due to several factors: a lack of simple methods for the analysis of the implicated food product for residues of commonly allergenic foods; uncertainty about the amount of food eaten; and questions about circumstances in the environment, such as possible other sources of the allergen. For example, in a case report by our group together with colleagues at the Mayo Clinic several years ago [11], a milk-allergic child apparently reacted after eating approximately 4 to 6 oz of sorbet containing less than 200 mg of whey protein. However, upon questioning, it was discovered that some members of the family were enjoying ice cream at the time of the incident. Many consumers reporting reactions simply throw away the food or it is disposed of in the stressful time surrounding the reaction and is not available for testing. While there are some data available in the literature on exposures causing allergic reactions and fatalities, the testing methods have not been fully validated. There are questions as to whether detection methods for allergens in processed foods may be truly quantitative. Therefore, the data must be viewed with caution and caveats. While such episodes reveal the hazards posed by undeclared residues of allergenic foods contaminating other foods, they are not particularly suitable for establishing the lowest provoking dose.

The methodology for detection of allergenic residues in foods is improving with the advent of enzyme-linked immunosorbent assays (ELISAs) for allergenic foods. These tests are most useful for application in the food industry, in assuring that raw ingredients, processing equipment, and products are free of undeclared allergenic residues. ELISA methods for peanut have been described for several years, and methods for peanut, milk, and egg have been commercialized into rapid test kits in the past few years. Methods for hazelnut, egg, sesame, and almond have been developed in recent years [12•] but are not yet commercialized, and methods for other allergenic foods are lacking. The development and use of these methods will make investigation of consumer complaints and gathering of data easier for determination of doses that cause reactions, but the reliability of the analytical results may be questioned until validated, collaboratively studied, well-accepted methods are available.

Conclusions

Threshold doses for allergenic foods have not been studied in depth to date but are an important part of risk assessment for the food industry. In addition, determination of threshold doses provides more accurate information to the food-allergic consumer as to his or her possible sensitivity

level. Thresholds may vary from individual to individual, and may be confounded by other factors, such as other medical conditions and alcohol consumption. Data gathered from DBPCFC research studies often are reported in ways that make it difficult to establish threshold doses for a particular allergenic food, although the data contained in these studies may be useful in designing threshold dose trials. Often, DBPCFC studies were done using different protocols, making estimation of threshold doses very difficult.

Clearly, sufficient results are available in the medical literature to conclude that the threshold doses for commonly allergenic foods are finite, measurable, and above zero. However, attempting to reach consensus on the threshold doses for the commonly allergenic foods at this time based on the existing data would probably be premature for a number of reasons. Given that the medical community recently has realized the benefit to the patient of challenging with low doses and also the need of the food industry for data on which to base risk assessment, it is anticipated that many more threshold studies will be performed in the near future. Development of an international standardized protocol for clinical threshold experiments is needed so that data can be compared and amassed in a logical way. Questions of criteria for patients to be included or excluded from threshold studies, appropriate forms of food to be used, and discussion of how to represent the data with regard to such factors as body weight need to be discussed. Standardization of various aspects of threshold studies would be helpful in obtaining easily comparable data from different clinics and research centers.

It is likely that some uncertainty will always remain regarding whether the threshold dose has been determined for the most sensitive individuals. Clinicians will never be completely certain that the most sensitive individual has been identified and tested. However, an analogy can likely be drawn to the infant formula industry where hypoallergenic infant formula based upon extensively hydrolyzed casein is safe for the vast majority of milk-allergic infants. Yet, hypoallergenic infant formula is known to elicit adverse reactions in a very small number of milk-allergic infants. This analogy illustrates the difficulty in developing threshold doses for all allergic consumers. Instead, the goal should be to identify threshold doses that protect the vast majority of allergic consumers. In summary, the threshold doses reported to date are in the low-milligram range. Occasionally, allergic individuals can (and probably do) ingest foods containing lower amounts of their offending food without any adverse reactions. Efforts should be undertaken as soon as possible to establish an international protocol for standardized clinical threshold studies so that lowest provoking doses for commonly allergenic foods are obtained employing as wide a range of affected patients as possible.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. •• Bock SA, Munoz-Furlong A, Sampson HA: **Fatalities due to anaphylactic reactions to foods.** *J Allergy Clin Immunol* 2000, **107**:191–193.

An in-depth look at 32 cases of fatalities due to foods and the surrounding circumstances.

2. Huggett AC, Hischenhuber C: **Food manufacturing initiatives to protect the allergic consumer.** *Allergy* 1998, **53**(suppl 46):89–92.
3. Yunginger JW, Sweeney KG, Sturmer WQ, *et al.*: **Fatal food-induced anaphylaxis.** *JAMA* 1988, **260**:1450–1452.
4. Sampson HA, Mendelson L, Rosen JP: **Fatal and near-fatal anaphylactic reactions to food in children and adolescents.** *N Engl J Med* 1992, **327**:380–384.
5. •• Hourihane JO: **The threshold concept in food safety and its applicability to food allergy.** *Allergy* 2001, **67**:86–90.

An opinion paper outlining some of the questions and considerations surrounding threshold studies by one of the first investigators to address threshold issues.

6. Hourihane JO, Kilburn SA, Nordlee JA, *et al.*: **An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study.** *J Allergy Clin Immunol* 1997, **100**:596–600.
7. Rance F, Abbal M, Dutau G: **Peanut allergy in children: skin prick test, specific IgE and dose response by double-blind placebo-controlled food challenge [abstract].** *Allergy* 2000, **55**(suppl 63):55.
8. Hansen TK, Bindslev-Jensen C: **Codfish allergy in adults. Identification and diagnosis.** *Allergy* 1992, **47**:610–617.
9. Christie L, Burks AW, Althage K, *et al.*: **Threshold dose for egg allergy determined by oral challenge [abstract].** *J Allergy Clin Immunol* 2001, **107**:S231.
10. Sicherer SH, Munoz-Furlong A, Burks AW, *et al.*: **Prevalence of peanut and tree nut allergy in the US determined by a random digit dial telephone survey.** *J Allergy Clin Immunol* 1999, **103**:559–562.
11. Laoprasert N, Wallen ND, Jones RT, *et al.*: **Anaphylaxis in a milk-allergic child following ingestion of milk-contaminated lemon sorbet.** *J Food Prot* 1998, **61**:1522–1524.
12. • Hefle SL: **Hidden food allergens.** *Curr Opin Allergy Clin Immunol* 2001, **1**:269–271.

A review of recent findings in the area of hidden food allergens.