



Perspective

Importance of establishing threshold levels for food allergens

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The concept of a threshold for provoking potential allergic reactivity is an important research target to pursue over the next 5 years. A food allergen threshold is defined as the eliciting dose or minimal quantified amount of ingested allergen that will provoke an immunologic (ie, IgE-mediated) reaction.¹ Defining such a zone will benefit multiple sectors of society: food allergic individuals, their caretakers, the food industry, policymakers, and government officials.^{1–3} This is a necessary strategy given the constraints of the current labeling laws and the reality that such levels may exist, can be defined at individual and population levels, and might improve quality of life through expanding food choices.^{4–7}

Currently, the Food Allergen Labeling and Consumer Protection Act (FALCPA; which went into effect in 2006) requires labeling of the common 8 allergens (milk, egg, wheat, soy, peanut, tree nut, fish, and crustacean shellfish) as an ingredient in packaged goods. The law also requires, for tree nuts, fish, and shellfish, that the specific food (eg, walnut, shrimp, etc) be identified.⁷

However, the FALCPA creates an exemption for trace allergen contamination that can occur during the production and packaging process within the same physical plant, sometimes even on the same production line.^{7,8} Precautionary statements, such as “may contain,” “made on shared equipment,” or “produced in a shared facility” create uncertainty because these statements do not definitively specify the risk in affirming the known presence of the major allergen.^{9–11} This risk ranges from a known, quantifiable inclusion to a proactive yet unnecessary overspecification of potential risk because the total absence of a particular allergen cannot be guaranteed.¹² Moreover, the FALCPA likely will not be amended to account for these exemptions or to add a declaration of

additional major allergens (eg, sesame); thus, the law will continue to create ambiguity.⁸

Precautionary statements force allergic consumers to balance the potential uncertainty of the risk of a reaction by ingesting such products against decreasing quality of life through additional restriction of packaged food items from their food choices. Medical providers generally advocate strict avoidance of any product with precautionary statements in the absence of firm knowledge of how sensitive some patients may be to even trace levels, on the assumption that some risk would potentially be taken if these products were eaten. However, it would be unwise for providers to assume that patients always follow such advice. Data show that many allergic consumers ignore precautionary labeling for different reasons: the product may have been safely consumed previously, thereby creating a false presumption of safety; misunderstanding of the language (“may contain” presumed as equal to “produced in a shared facility”); or just outright disregard for the potential risk.^{9,13} This is a potentially dangerous scenario, considering evidence that these products frequently do contain the allergen on the level of parts per million.^{9,11,14} Some individuals may be exquisitely sensitive to such minute quantities.

A threshold level can be established at an individual patient level (a lowest observed adverse effect level [LOAEL]) or at a population level (referred to as an “eliciting dose” [ED]).⁵ Proposed strategies have included establishing an ED level at which no reaction is seen or a level at which only a minority of patients (eg, 5%, 10%, etc) react.¹⁵ A 0-risk level is unrealistic and likely could not be established.² Data are available from published studies of food challenges and day 1 rapid-desensitization phase from oral immunotherapy studies that could be used to help establish a target level for a threshold.^{5,15,16} In fact, the US Food and Drug Administration (FDA) has considered a probability-based model for a LOAEL to establish a cutoff at which only 5% (ED5) of the population might react.¹⁷ However, using published data makes such a level susceptible to the biases and limitations inherent to the findings of those underlying studies (eg, numerous facets of selection bias, poor experimental design, difference in challenge

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technique, and potentially unmeasured patient-level attributes between challenged and unchallenged populations); these limitations would be compounded in aggregate and potentially affect the validity of an established threshold level.^{5,18}

There are poor data describing patient understanding of what a threshold level represents, how the information could be used, and the role industry would play. The results of a 4-question survey gauging consumer perception of threshold levels administered at a Food Allergy and Anaphylaxis Network (now the Food Allergy Research and Education [FARE]) conference showed poor consumer insight into threshold levels and little knowledge about how thresholds may affect precautionary labeling (C. Weiss, personal correspondence, April 18, 2013). A more recent internet survey administered on the FARE Web site in the fall of 2012 noted that 64.8% of respondents indicated that they would not buy products containing the allergen even if it would not trigger a reaction, indicating that acceptance of threshold levels among patients may be a challenge.¹⁹

However, it would be wrong for the medical community to assume that patients would not be interested in better understanding the threshold concept. In fact, there is evidence that patients may be casually experimenting with discovering their own thresholds by eating products with precautionary allergen statements.^{9,13} Furthermore, it is important to note that the food industry is a valuable stakeholder in the situation and wants to establish and provide data to aid consumers. Several key industry persons, government representatives, and consumer groups from around the world attended and advocated for the sharing of this information at a Preventive Controls Symposium cohosted by the Food Allergy and Anaphylaxis Network (now FARE) and the Global Food Protection Institute in September 2012 (M. Greenhawt and C. Weiss, personal communication, April 18, 2013). However, it remains unresolved about how to best provide a consistent and accurate reported level and the extent to which regulation will be needed to ensure such reporting.^{2,16}

What is the best way to accomplish these tasks? A multicenter prospective approach, using a common protocol and broad inclusion criteria, would be the most valid means of establishing threshold levels on a population level. Such a study should incorporate a double-blinded, placebo-controlled challenge using a multilevel design to decrease the effects of clustering, not be over-reliant on excluding individuals based on presumed past reaction severity or serum-specific IgE levels/skin tests in excess of certain values (eg, 95% diagnostic decision points or with a history of anaphylaxis), and include as many centers as possible to ensure a robust sample is studied and proper confidence intervals around the threshold level can be established.^{4,5,15,18} In addition, a replication cohort could be part of the design to revalidate the findings. It would further behoove the investigative team to partner with industry and government to make sure their considerations as stakeholders are addressed. A LOAEL, established from a small trial involving a limited number of centers, would have limited utility, and the danger from such a study would be to assume that the LOAEL could generalize to a true ED₅ or ED₁₀.^{1,2,15} Without obtaining a robust and diffuse sample, there would be the danger of failing to determine how heterogeneous the threshold tolerance may be within the food-allergic population.¹⁵

The advantages to establishing a threshold dose are numerous. This is an empowering step that will increase the number of available products for food-allergic individuals. This could improve quality of life and lessen anxiety, which are tied to the perception of dietary freedom.^{20–22} Enhanced dietary freedom also may improve nutrition for some individuals. For industry, proper, accurate labeling could increase revenue by attracting new consumers. For the medical community, threshold dosing will help provide risk stratification and understanding of the heterogeneity of food

allergy as a disease across the population (ie, the disease does not follow a straight line but is differentially manifest across the population) and might decrease overall patient anxiety regarding eating packaged foods. Moreover, thresholds will help the FDA issue science-based, appropriate performance standards for allergens as mandated by the Food Safety Modernization Act.²³ Thus, this is a rare case of great potential for a win-win-win-win strategy for all stakeholders.

Establishing an allergen threshold dose is not without potential problems. Foremost, there is risk of provoking a reaction when introducing a potential food allergen, a point that has dictated a rather risk-averse climate among allergists toward challenging certain individual profiles (eg, patients with high serum IgE levels/large skin tests or history of a severe reaction).²⁴ The proposed experimental design may result in too small or too clustered a sample to extrapolate the findings to a true population level, resulting in an inaccurate result and potentially catastrophic false sense of security. It is unclear how willing patients (or their caretakers) might be to consent to participation or how many would trust such established levels for their individual situation.²⁵ Furthermore, industry's response is unknown—would labeling become more transparent (with exact parts per million or weight-based declaration of quantity) and how would that be audited and enforced? Without regulatory and medically recognized reference doses demonstrating acceptable levels of risk for major allergens, manufacturers and the food service industry may not be willing to embrace and practice the concept.^{1,2} Industry relies on testing methods based on commercial enzyme-linked immunosorbent assays to detect allergen residues to validate their allergen control programs.^{9,11,14} Although substantial progress has been made in the development and use of these tests, further efforts are needed to develop methods for allergenic foods, to improve and standardize existing measurement techniques, and to lower the cost of such methods, thereby expanding their use and acceptability, especially by smaller manufacturers. A unified technique would help to provide an industry standard.

Choice of target foods also would be somewhat controversial. Allergens not covered under the FALCPA (eg, sesame) should not necessarily be overlooked, although it would not be practical to establish a threshold for every single potential food allergen.¹⁶ Limited data exist as to which allergens pose the greatest health risk to an individual or are associated with the most diminished quality of life, and investigators should be wary of making a choice of targets based on which allergens are simply the most prevalent or what experts perceive are the greatest threats (ie, this process should be data driven).^{1,26} Educational awareness training for the affected populations (consumers, physicians, regulators, industry, etc) is another challenge, because many stakeholders are largely unaware of the advances in research regarding the threshold concept and have advocated a “strict avoidance” mentality for years.^{9,16} For successful adaptation and implementation, this avoidance paradigm would have to be modified, and ultimately these changes would have to be accepted and not viewed as risky by the food-allergic community.²⁵ The regulatory framework for implementing threshold doses to food labeling also will pose challenges, and this particular implementation process is likely to be methodical, involving multiple government agencies (the FDA, the US Department of Agriculture, and Congress among others). Food challenges in the clinical setting, still the backbone of how a threshold dose would be established, are time consuming and labor intensive and would present a costly new mandate for the health care system. Efficient, cost-effective, and minimally intrusive approaches for determining the threshold dose of the individual patient must still be developed. Medical professionals must then be able to effectively counsel patients based on this new information. Table 1 presents a comprehensive list of potential problems with the establishment of thresholds.

Table 1

Potential arguments against establishing threshold levels for food allergy reactivity

Argument	Stakeholder affected	Reasoning
A LOAEL is highly patient specific, may be affected by numerous patient level factors, and may not be consistent on a day-to-day basis	patient, provider, industry, government	Numerous factors can affect a food challenge (eg, infection, medication use, ETOH use, exercise, etc). The LOAEL differs among patients and may differ within the same patient on different days (eg, may require multiple sequential challenges to establish a consistent level, will vary by country).
It is not feasible to reliably establish an ED for the population based on current data or to conduct a large, population-based study to determine this	patient, provider, industry, government	Establishing an ED for any confidence level (1%, 5%, 10%) will require a study with a complex multistaged sampling frame, hierarchically modeled, and conducted broadly over a truly representative population. There is no precedent in the United States for such a study to be conducted in allergy. Not every child could have a particular LOAEL determined and it is unclear who could/would provide funding. Is it ethical to set a threshold if some portion of the population will not be protected? We do not have an accurate assessment of prevalence of food allergy in the United States, using challenge as the gold standard for diagnosis.
Our society is too litigious to accept the risk of establishing a LOAEL or ED	patient, provider, industry, government	Practice environment is very conservative and wary of malpractice. We have set a standard of care of avoidance at all cost. We have a risk-averse conservative approach to food challenge (eg, 50% and 95% PPVs). Who would legislate or enforce the process or regulate and standardize the reporting process? There may be considerable international variation. Who holds the responsibility? We have preached total avoidance and minimization of any risk, and patients have trusted this advice.
This contradicts the avoidance model, and both parents and some providers may be slow or unwilling to trust that a threshold can be safely established	patient, provider	It is uncertain how much risk a parent or patient will be willing to undergo (eg, tolerance of “mild” symptoms) or what degree of trust they will have in these levels. Will consumers trust industry? Will all providers buy into the concept?
The process is cost prohibitive	patient, provider, industry, government	Establishing an ED at a population level would require a very expensive study. Costs of measuring, detecting, and labeling may exceed net profit to the company in terms of new consumers.
Long-term effects are unknown	patient, provider, industry, government	It is unknown if subacute, chronic exposure to an allergen is associated with the development of eosinophilic esophagitis or regression of tolerance (eg, OIT data). If a threshold is improperly set, there may be other wide ranging effects.
Evidence exists that some patients may not support the idea that thresholds are safe or that thresholds would be beneficial	patient, provider, industry, government	Recent FARE survey and comments to the FDA indicate patient and caregiver distrust and reluctance. ^a To what extent would the diet need to be liberated to produce a meaningful change in patients? Sentiment and desire to establish this concept may differ by country.

Abbreviations: ED, eliciting dose; ED5, eliciting dose of 5%; FARE, Food Allergy Research and Education; FDA, US Food and Drug Administration; LOAEL, lowest observed adverse effect level; OIT, oral immunotherapy; PPV, positive predictive value.

^aThreshold of regulation exemptions listed by the FDA (<http://www.fda.gov/Food/IngredientsPackagingLabeling/PackagingFCS/ThresholdRegulationExemptions/ucm093685.htm>) and survey on food allergies and thresholds by FARE (<http://www.foodallergy.org/document.doc?id=208>).

Overall, government, industry, the medical community, and food-allergic patients and caregivers should enthusiastically embrace the opportunity to establish reactivity thresholds. Such knowledge will produce enormous net benefit to all parties and tightly specify patients at the highest risk. Enhancing food labels with allergen threshold information will expand dietary options for patients, which will improve quality of life. More importantly, establishing thresholds will correct deficiencies in the FALCPA. There may be hypothesized long-term immunologic benefit to selected patients from subchronic exposure to a threshold level that may hasten the resolution of their food allergy. This is the rare instance when all stakeholders can derive mutual benefit from a concept, with minimal risk.

Considerable progress on thresholds has been made in the past 5 to 7 years thanks to the efforts of clinicians, public health officials (including the FDA Threshold Working Group), academic scientists such as those in the Food Allergy Research and Resource Program and the Netherlands Organization for Applied Scientific Research, consumer organizations, and the food industry. These efforts and the scientific data gathered to date represent an appropriate foundation from which to move forward.

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