

Correspondence

Reply

To the Editor:

The limitations of threshold doses established in the “sterile” environment of the clinic, in which those with a history of anaphylaxis have been explicitly excluded, have long been recognized.^{1,2} Consequently, it has been our view, and that of others involved in food allergen risk management, that simple extrapolation of ED10 doses defined by dose distribution modeling using data from low-dose threshold challenge studies is not sufficient for identifying regulatory action levels for allergens in foods.^{1,2} Indeed, ED01 and ED05 values may be more appropriate and have been used in the Voluntary Incidental Trace Allergen Labelling (VITAL) 2.0 thresholds recommended for use in Australia.³ Validation of the dose distribution modeling on which the VITAL thresholds are based is underway for peanut in the Peanut Allergen Threshold Study,⁴ using single-dose challenges set at the ED05 level to check whether it is an appropriate value for public health measures. The data from our article,⁵ together with the data used for VITAL,³ are also now being validated at the ED05 level for hazelnut, egg, and milk through the Integrated approaches to food allergen and allergy management (iFAAM) project (<http://www.inflammation-repair.manchester.ac.uk/ifaam>). Exclusion criteria for single-dose challenges are different, and in the Peanut Allergen Threshold Study patients with anaphylaxis are excluded only if they have had a reaction within 4 weeks before the study challenge. This makes the food-allergic population used for validation of the ED05 values more representative of the population as a whole, and overcomes one of the limitations of classical low-dose threshold challenge studies.

As Lieberman⁶ rightly points out in his correspondence, there are many factors that may affect both the dose at which a food-allergic individual may have a reaction and the pattern and severity of the ensuing reactions. The unpredictable nature of allergic reactions is one of the challenges facing both patients and their health professionals. How rigorously should patients practice food avoidance? Should they be prescribed rescue medication? Gaps in our knowledge regarding extrinsic factors and their role in determining the severity of reactions of major allergenic foods, such as peanut, are inevitably hampering our efforts to include variability in clinical reactivity to foods in allergen risk management strategies.⁷ Studies are underway in the United Kingdom (TRACE; <http://www.tracestudy.com/about>) and across Europe (iFAAM) that will provide missing data on the reproducibility of an individual's threshold responses, and define the impact of factors, such as exercise and stress (TRACE), the food matrix, and proton pump inhibitors (iFAAM) on both threshold dose and severity of reaction. These investigations will provide risk assessors and managers with evidence to support decisions such as the choice of either an ED01 or an ED05 reference dose as the basis for a regulatory action level. Establishing how data on reactivity to foods gathered in a clinical setting relates to reactions in the community is also important, but difficult to determine. Nevertheless, approaches have been developed to study the circumstances whereby food-allergic patients experience reactions in their everyday life and are being applied in The

Netherlands and the iFAAM project.⁸ These studies will provide important insights into whether such reactions are due to the presence of trace amounts of allergens, poor control of associated conditions, such as asthma, or lack of vigilance in avoiding problem foods.

Food allergens have presented a new paradigm in food safety, requiring the development of novel risk assessment and management approaches that differ from many other chemical hazards found in food. Although some level of uncertainty and risk will always remain, the approaches being developed have the advantage of being based on data from human allergic subjects, and will not have to address the uncertainties inherent in extrapolating from animal model data, as is generally the case for food chemical hazards. Information on extrinsic factors, validation of threshold dose distributions, and studies of allergic reactions experienced in the community will provide a firm evidence base on which to establish any future action levels for allergens in foods that might trigger the use of precautionary labeling,⁷ and regulatory limits that define “allergen free,” in a manner similar to that established for “gluten-free” foods. Last, a close collaboration between health care professionals, patient groups, food scientists, and risk assessors and regulators will be essential to ensure that when precautionary labeling does have to be applied, its meaning and relevance for patients are clear and enables them to make safe food choices.

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