Allergen reference doses for precautionary labeling (VITAL 2.0): Clinical implications

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Background: There has been a dramatic proliferation of precautionary labeling by manufacturers to mitigate the perceived risk from low-level contamination from allergens in food. This has resulted in a significant reduction in choice of potentially safe foods for allergic consumers.
Objectives: We aimed to establish reference doses for 11 commonly allergenic foods to guide a rational approach by manufacturers based on all publically available valid oral food challenge data.
Methods: Reference doses were developed from statistical dose-distribution modeling of individual thresholds of patients in a dataset of more than 55 studies of clinical oral food challenges. Sufficient valid data were available for peanut, milk, egg, and hazelnut to allow assessment of the representativeness of the data used.
Results: The data were not significantly affected by the heterogeneity of the study methodology, including little effect of age on results for those foods for which sufficient numbers of adult challenge data were available (peanut and hazelnut). Thus by combining data from all studies, the eliciting dose for an allergic reaction in 1% of the population estimated for the following were 0.2 mg of protein for peanut, 0.1 mg for cow's milk, 0.03 mg for egg, and 0.1 mg for hazelnut.
Conclusions: These reference doses will form the basis of the revised Voluntary Incidental Trace Allergen Labeling (VITAL) 2.0 thresholds now recommended in Australia. These new levels will enable manufacturers to apply credible precautionary labeling and provide increased consumer confidence in their validity and reliability, as well as improving consumer safety. (J Allergy Clin Immunol 2014;133:156-64.)

Key words: *Food allergy, allergen thresholds, peanut, egg, cow's milk, soy, hazelnut, precautionary labeling*

Food allergies are increasing in prevalence, and severe reactions are occurring more frequently.[1] Currently, the mainstay of food allergy management is complete avoidance of all foods that contain the causative allergen. To this end, most developed countries now mandate labeling of the most common allergenic foods: peanuts, tree nuts, milk, eggs, sesame, fish, crustaceans, mollusks, soy, and wheat or cereals containing gluten, as well as ingredients derived from those foods.[2]

Despite the best efforts of manufacturers, allergens can occur unintentionally in foods through cross-contamination from the use of shared equipment and facilities or from issues related to the supply chain of ingredients. Uncertainty over the risk posed by even very small residual amounts of allergen and its effect on allergic consumers prompted manufacturers to introduce precautionary (advisory) labeling (eg, "may contain"). Application of precautionary labeling currently remains inconsistent across industry and products. Furthermore, multiple phrases are used, which allergic consumers invest with different risk significance.[3] Yet analytic evidence shows that no basis exists for such differences.[4-8] This proliferation and increased variety of types of precautionary labeling have reduced the food choices for allergic consumers. This has resulted in increased risk taking among allergic consumers because of the ubiquity of labeling, with one study recently showing that more than 65% of all edible goods in an Australian supermarket setting have some form of precautionary labeling.[3] The overuse of precautionary labeling places severe restrictions on dietary choices for consumers.[6,9]

Establishment of a reliable labeling system that is informed by evidence and practical to use will not only enhance the safety and credibility of precautionary labeling but also enable manufacturers to minimize its overuse through a formal risk assessment tool. This will in turn provide increased consumer confidence in their validity and reliability and enable allergic consumers to eat a wider variety of food with safety and confidence.

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This study was conducted within the framework of the Food Safety Knowledge Development program of TNO, with financial support from the Dutch Ministry of Health, the Allergen Bureau of Australia (www.allergenbureau.net), the Victorian Government's Operational Infrastructure Support Program, Australia, and the Food Allergy Research & Resource Program (FARRP), University of Nebraska, Lincoln, Nebraska. K.J.A. is a Charles and Sylvia Viertel Senior Medical Research Fellow.

Disclosure of potential conflict of interest: K. J. Allen is a board member for Ilhan food allergy foundation, and has received payment for lectures, including service on speakers' bureaus, from Pfizer, Nutricia, Annual Women's Update, and Abbott. B. C. Remington, J. L. Baumert, and S. L. Taylor have received grants from multiple food companies (70 in total; the Food Allergy Research & Resource Program is an industry-funded consortium. This funding was used to support this study and publication, but food companies do not control the design or results of the study). R. W. R. Crevel is employed by and has stock in Unilever PLC. G. F. Houben has received money for his institution from the Dutch Ministry of Health. S. Brooke-Taylor has received a consulting fee or honorarium from and has consultant arrangements with The Allergen Bureau, Australia. A. G. Kruizinga has received research support from the Dutch Ministry of Health and is employed by TNO.

Received for publication December 13, 2012; revised June 20, 2013; accepted for publication June 21, 2013.

Available online August 26, 2013.

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0091-6749/$36.00

http://dx.doi.org/10.1016/j.jaci.2013.06.042

Abbreviations used
ED: Eliciting dose
FARRP: Food Allergy Research & Resource Program
GLRT: Generalized log-rank test
LOAEL: Lowest-observed-adverse-effect level
NOAEL: No-observed-adverse-effect level
VITAL: Voluntary Incidental Trace Allergen Labeling

Definition of thresholds for the management of allergens has been recognized to be of considerable value to all stakeholders,[10] but in the past, there have been insufficient data to adequately derive thresholds.[11] The Voluntary Incidental Trace Allergen Labeling (VITAL) initiative developed by the Australian food industry's Allergen Bureau represented a first attempt to introduce a formal and transparent basis for application of precautionary labeling.[12] A key feature of the system was the development of the VITAL grid, in which action levels (in parts per million) were defined for major allergenic foods. The initial VITAL action levels were based on minimum provoking doses for regulated allergenic foods (expressed as doses of protein) collated by the 2006 US Food and Drug Administration Threshold Working Group together with the assumption of a consumption amount of 5 g. Because limited data on minimum provoking doses existed at that time, a 10-fold uncertainty factor was applied by VITAL to ensure that sufficiently conservative action levels were promulgated.

As part of a major revision of VITAL, a scientific panel of international experts recently reviewed the action levels defined in the original VITAL grid in light of the considerable volume of data and knowledge that emerged on thresholds and risk assessment of allergenic foods in recent years. The express intention of this exercise was to improve the quality of VITAL guidelines on use of precautionary labeling to optimize its usefulness for consumers. The approach of this expert panel to the derivation of appropriate reference doses using statistical modeling has been published in detail elsewhere.[13,14] This article briefly presents those recommendations while expanding on key clinical aspects and the implications for management of patients with food allergy.

METHODS

In late 2010, all available data on individual no-observed-adverse-effect levels (NOAELs) and lowest-observed-adverse-effect levels (LOAELs) from clinical oral challenge trials were collated independently by both the Food Allergy Research & Resource Program (FARRP) and TNO (Zeist, The Netherlands) from both published and unpublished sources. The clinical literature was searched by both FARRP (B.C.R. and J.L.B.) and TNO (A.G.K.) independently by using key words, including "allerg*," "threshold," "oral food challenge," "double-blind placebo-controlled food challenge," "minimum eliciting dose," and the 11 respective allergens used for threshold development, to obtain published studies that could be evaluated for clinical threshold data that fit our selection criteria, as outlined below. Clinical threshold data for 11 priority allergens were obtained from 57 published studies and 6 further datasets from allergy clinics (unpublished clinical data, see Table E1 in this article's Online Repository at www.jacionline.org). The unpublished data from FARRP-sponsored threshold studies were obtained after obtaining informed consent of the subjects participating in the oral food challenge studies and approved by the respective medical ethics boards where the challenge studies were performed. The unpublished data from Wilhelmina Children's Hospital of the University Medical Center Utrecht, Utrecht, The Netherlands; University Medical Center Utrecht, Utrecht, The Netherlands; University Medical Center Groningen, Groningen, The Netherlands; and Universitätsmedizin Berlin, Berlin, Germany, were either obtained for diagnostic purposes or were obtained through threshold studies with informed consent of the subjects and approval by the respective medical ethics boards where the challenge studies were performed. The coded data were provided to TNO with the permission to use these data for this work. Permission was given by A. C. Knulst, MD, PhD, University Medical Center Utrecht, for data referenced from University Medical Center Utrecht, Utrecht, The Netherlands; Y. Meijer, MD, University Medical Center Utrecht, for the data references from Wilhelmina Children's Hospital of the University Medical Center Utrecht, Utrecht, The Netherlands; A. E. J. Dubois, MD, PhD, for data referenced from University Medical Center Groningen, Groningen, The Netherlands; and M. Worm, MD, PhD, for data reference from Charité, Universitätsmedizin Berlin, Berlin, Germany. Subsequently, the 2 sets of data were merged and reviewed by FARRP (B.C.R. and J.L.B.) and TNO (A.G.K. with assistance from E. Dutman and H. Buist) to ensure uniformity. The panel then held a meeting in January 2011 in Sydney (Australia) to develop a consensus approach for analysis of the available data.

Data selection and quality

The panel elected to use data from clinical oral food challenges from both published and unpublished studies, provided those data met quality criteria. Challenge data on as many of the priority allergenic foods as possible from the lists of Australia, the European Union, and the United States were included. Publications were selected based on the criteria outlined in Taylor et al,[15] in particular focusing on results from low-dose oral challenges to ensure the lower limits of the reference doses were well informed and avoiding an excessive proportion of low-dose reactors. Allergic patients from published and unpublished clinical studies were considered for inclusion in the dataset on the basis of a clinical history of reaction to the allergenic food and other diagnostic tests (positive skin prick test response, positive allergen-specific serum IgE test result, or both) in addition to a positive oral food challenge result. Additionally, the studies needed to describe the data in sufficient detail to discern individual data points and at least an individual LOAEL but preferably also an individual NOAEL. Studies were not included when the dose progression started so high that a large proportion of subjects reacted at the first dose. Data from studies in adults and older children (>3.5 years) were only included if they were generated by using a double-blind, placebo-controlled food challenge protocol, which is generally agreed by clinicians to be the gold standard for such studies.[16] Open oral food challenges were deemed acceptable for younger infants because only objective signs are used, and these are regarded as sufficiently reliable. The studies also generally used the first objective (externally observable) sign as the stop criterion for defining the LOAEL. This criterion is also widely considered the more reliable end point in such circumstances. In addition to the NOAEL and LOAEL, the symptoms experienced by each patient at the LOAEL, the age of the patient, and the geographic origin of the patient were recorded where possible. The nature of the challenge materials and the dosing regimen used in the challenges were also recorded for each challenge.

Analytic approach

The panel adopted a dose-distribution modeling approach, as described by Crevel et al,[17] together with interval censoring survival analysis, as used by Taylor et al.[15,18] This approach is widely accepted as one that uses the available data most effectively,[11,19] and interval censoring survival analysis permits the use of data points from first-dose reactors (left-censored observations), as well as those not reacting at the highest dose (in cases in which allergy is nonetheless independently proved [right-censored observations]). Data were analyzed both as discrete and cumulative doses and modeled by using log-normal, log-logistic, and Weibull distributions because no evidence exists to prefer one over the other from a biological point of view.[17] Where possible, populations (study population, geographic region, age, and challenge material) were analyzed nonparametrically by using the generalized log-rank test (GLRT) for interval-censored data[20,21] through the ICSTEST macro (SAS version 9.2; SAS, Institute, Cary, NC)[22,23] to determine whether the populations were significantly different ($P < .05$).

In selecting the recommended reference dose, weight was given to the goodness of fit for each parametric fit (as determined by the log likelihood), as well as visual examination of the fitted probability dose-distribution curves to