

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

Katrina J. Allen, MD, PhD, FAAAAI,^{a,b,c} Benjamin C. Remington, BS,^d Joseph L. Baumert, PhD,^d Rene W. R. Crevel, DIBT,^e Geert F. Houben, PhD,^f Simon Brooke-Taylor, PhD,^g Astrid G. Kruizinga, MSc,^f and Steve L. Taylor, PhD^d *Parkville, Melbourne, and Hobart, Australia, Lincoln, Neb, Bedford, United Kingdom, and Zeist, The Netherlands*

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.

From ^athe Murdoch Childrens Research Institute, Parkville; ^bthe Department of Paediatrics, University of Melbourne; ^cthe Department of Allergy and Immunology, Royal Children's Hospital, Parkville; ^dthe Food Allergy Research & Resource Program (FARRP), University of Nebraska, Lincoln; ^ethe Safety & Environmental Assurance Centre, Unilever, Colworth Science Park, Sharnbrook, Bedford; ^fTNO, Zeist; and ^gthe Allergen Bureau of Australia, Hobart.

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Corresponding author: Katrina J. Allen, MD, PhD, FAAAAI, Murdoch Childrens Research Institute, Royal Children's Hospital, Flemington Rd, Parkville, Victoria 3052, Australia. E-mail: katie.allen@rch.org.au.

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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

the actual individual threshold data within the low-dose zone, which is the zone of relevance to public health protection. Thus the reference dose is not a simple mean of the chosen EDs from each distribution but involves expert judgment. The dose distributions for individual subject thresholds were modeled separately for each allergenic food by using all 3 statistical probability dose-distribution models (log normal, log logistic, and Weibull). In each case the model with the best statistical fit was determined along with visual examination to determine the best fit at the low doses, which are critical to the analysis, as described by Blom et al.²⁴ The challenge doses were normalized in all cases to milligrams of protein from the allergenic food by using conversions outlined in Table E2 in this article's Online Repository at www.jacionline.org.

In formulating its recommendations, the panel finally decided to express its recommendations as reference doses, which were defined as amounts of allergenic protein associated with defined levels of protection based on the dose-distribution modeling for each allergen.

RESULTS

Datasets

Data from large numbers of subjects ($n > 200$) were only available for peanut, milk, egg, and hazelnut. Smaller amounts of individual threshold data ($n < 80$) were found for soybean, wheat, cashew, mustard, lupin, sesame seed, shrimp, celery, and fish. The number of data points needed to derive reference doses based on specific ED values from population dose distributions of thresholds (minimal EDs) with adequate statistical confidence has not been defined.^{17,24} However, as discussed by Crevel et al,¹⁷ low-dose extrapolation beyond the point of the distribution for which data points exist is best avoided because this results in the statistical model used having a greater influence on the derived ED value than the actual data. Detailed evaluation of each dose-distribution model for each allergen was conducted, as described earlier. On the basis of the tight fits of the 95% upper and lower CIs, the expert panel determined that threshold datasets containing more than 200 data points were suitable for derivation of reference doses based on the ED₀₁ value, which was defined as predicted ED for the most sensitive 1% of the population. The 95% upper and lower CIs were much wider for datasets containing 80 or fewer subjects (particularly in the low-dose area of the curve), and therefore less statistical confidence exists for derivation of reference doses based on the ED₀₁ value. The expert panel chose to use the 95% lower CI of the ED₀₅ value for datasets containing less than 80 subjects to provide more statistically sound estimations for derivation of reference doses. The reference doses are presented in Table I and are based on ED₀₁ values for foods with large numbers of subjects (peanut, milk, egg, and hazelnut) and the 95% lower CI of the ED₀₅ for foods where individual threshold data were found for smaller numbers of subjects (soybean, wheat, cashew, mustard, lupin, sesame seed, and shrimp). Full details of derivation of the VITAL reference doses are described elsewhere.^{13,14} The individual threshold data for celery and fish were insufficient to allow modeling, and therefore reference doses could not be established for those 2 foods. Among the priority allergenic foods on the Australian, European Union, and US lists, no threshold data were found for tree nuts other than hazelnut and cashew (children only) or for molluscan shellfish at the time of the expert panel's review, and therefore reference doses could not be established for those foods either. Blom et al²⁴ recently published individual threshold data from 13 children with walnut allergy; however, only 4 of these children met our inclusion criterion of objective end point symptoms on oral

challenge, which is insufficient for statistical dose-distribution modeling and derivation of a reference dose for walnut.

Assessment of validity among heterogeneous data

Study population. The quality of the reference doses is dependent on the representativeness of the patient population. For peanut and cow's milk, individual threshold data were available from low-dose oral challenges conducted for diagnostic purposes, as part of threshold studies, and from the baseline evaluations in immunotherapy trials, and sufficient data are available for peanut and these foods to allow a comparison of these sources (Fig 1, A). Study populations of patients with peanut allergy were significantly different, as determined by using the GLRT. Examination of the ED₀₅ estimates revealed similar ED₀₅ estimates for diagnostic and threshold challenges and for threshold and immunotherapy challenges. However, ED₀₅ estimates for immunotherapy trials were significantly lower than those for diagnostic challenges (0.4 mg of peanut protein for the immunotherapy group, 0.9 mg for the threshold group, and 2.0 mg for the diagnostic group). This analysis indicates that the selection of patients with peanut allergy for immunotherapy trials is biased toward more sensitive subjects but not dramatically so compared with threshold studies. The difference between the immunotherapy and diagnostic groups is more evident for milk (Fig 1, B). The immunotherapy and diagnostic populations have similar ED₀₅ values of 1.3 and 3.6 mg of milk protein, respectively, but statistically different ED₁₀ values of 2.6 and 13.0 mg of milk protein. However, this example shows clearly that the shape of the dose-distribution curve has only small effects on ED₀₅ estimates when data from reasonably large numbers of patients are involved.

Geographic comparison. Sufficient numbers of patients from clinical studies were available to allow a limited geographic comparison of the data from several countries, including peanut from France, The Netherlands, the United Kingdom, and the United States and milk from The Netherlands, Italy, and Australia (Fig 2). Populations of patients with peanut allergy from France, The Netherlands, the United Kingdom, and the United States were significantly different, as determined by using the GLRT. The ED₀₅ estimates from France, The Netherlands, and the United States are not substantially different, falling between 2.0 and 4.0 mg of peanut protein. The ED₀₅ value is significantly lower for the United Kingdom group (0.2 mg of peanut protein), but the challenge data came from threshold and immunotherapy studies and might thus reflect a patient's selection bias toward more sensitive subjects. Overall for milk, populations of allergic patients from The Netherlands, Australia, and Italy were significantly different, as determined by using the GLRT. The ED₀₅ and ED₁₀ estimates for The Netherlands and Italy (1.9 and 2.0 mg of milk protein, respectively) were not significantly different. The ED₀₅ value for Australia is significantly higher (69.5 mg of milk protein) compared with those from The Netherlands and Italy. However, the Australian data are entirely obtained from Hill et al,²⁵ in which the initial challenges began at 66 to 300 mg of milk protein, a level somewhat higher than subsequent protocols used in The Netherlands and Italy. This finding illustrates the importance of data from challenges using very low doses in obtaining the best estimates of ED values. By combining data from various countries and multiple clinics, the effects of possible patient selection biases, clinical protocol differences, and other factors

TABLE I. Newly revised VITAL 2.0 scientific expert panel recommended reference doses

Allergen	Proposed ED	Protein level (mg)	Equivalent dose per serving size
Peanut	ED ₀₁	0.2	1/1000 of a whole peanut kernel*
Cow's milk	ED ₀₁	0.1	1:320 th of 1 mL of cow's milk†
Egg	ED ₀₁ and lower 95% CI of ED ₀₅	0.03	1:200,000 of a raw egg white‡
Hazelnut	ED ₀₁ and lower 95% CI of ED ₀₅	0.1	
Soy	Lower 95% CI of ED ₀₅	1	
Wheat		1	
Cashew		2 (provisional)	
Mustard		0.05	
Lupin		4	
Sesame		0.2	
Shrimp		10	

*Equivalent dose is based on the average weight of a roasted peanut kernel (700 mg) and assumes that whole peanut contains 25% protein based on data from the United States Department of Agriculture National Nutrient Database.

†Assumes fluid milk contains 3.3% milk protein based on data from the United States Department of Agriculture National Nutrient Database.

‡Equivalent dose based on the average weight of a hen's egg (50 g) assumes a hen's egg contains 12.6% protein based on data from the United States Department of Agriculture National Nutrient Database.

are diminished, and all data can be used to inform selection of the ED value.

Effect of age. Individual threshold data were combined for children and adults to provide sufficient data for modeling. The assumption is thus made that the EDs for populations of children and adults do not differ. Sufficient data are available for peanuts and hazelnuts to assess differences between children and adults. Although large numbers of patients were also available for cow's milk and eggs, the vast majority of subjects were children, as would be expected because children often outgrow their milk and egg allergies over time.²⁶ Fig 3 shows the comparison of the dose distributions for adults and children for peanuts and hazelnuts, respectively. Although the overall distribution curves of adults and children with peanut allergy were significantly different, as determined by using the GLRT, and children seem to be somewhat more sensitive than adults to peanut (Fig 3, A), the ED₀₅ and ED₁₀ estimates of 2.3 mg of peanut protein for adults and 1.7 mg of peanut protein for children were not significantly different. Because the more conservative ED values are the primary focus for derivation of reference doses, it would be expected that these would protect both children (including infants, children, and adolescents) and adults with peanut allergy.

For hazelnuts, no significant difference between adults and children was determined by using the GLRT, but the ED₀₅ estimates are actually somewhat more variable, with adults at 4.0 mg and children at 1.2 mg of hazelnut protein (Fig 3, B). Combining data from adults and children seems reasonable for peanuts and hazelnuts based on the modest differences, especially at the lower end of the distribution curve, which is used for derivation of reference doses. More information will need to be collected for adults for milk and egg to allow comparisons according to age.

Variations in challenge methodology. The 2 most critical variables in the oral challenge protocols were the dose progression and selection of the challenge materials. The selection of data from low-dose challenge trials was essential to limit the number of left-censored subjects (first-dose reactors) and to ensure that any left-censored subjects would be found at comparatively low doses. The use of interval censoring survival analysis¹⁵ allowed easy adjustment for differences in dose progressions, although the use of tighter dose intervals improves the estimate of any individual threshold. The doses can be presented as either discrete or cumulative doses. Clearly, individual

doses are not likely to be totally assimilated in the short period (usually 15-20 minutes) between doses. When the dose distributions and ED values were compared on the basis of discrete versus cumulative doses, minimal differences were observed (data not shown).

Dose normalization of protein content. All doses were normalized on the basis of protein from the allergenic source. Such normalization was necessary because differences existed in the choice of challenge materials. When combining data from all challenges, the assumption was made that the nature of the challenge material did not have any influence. Sufficient data were available for peanut to allow a comparison of predicted ED₀₅ values for challenges using pulverized roasted peanuts and partially defatted, lightly roasted peanut flour (Table II).²⁴⁻²⁶ Overall, these 2 peanut sources were significantly different, as determined by using the GLRT; however, no significant difference was found when comparing the estimated ED₀₅ and ED₁₀ values, and only the ED₅₀ value was significantly different for the 2 peanut sources. For milk, sufficient data existed to compare liquid milk and nonfat dry milk (Table II), and these 2 sources were equivalent by using both the GLRT and ED comparisons.

Sufficient data also existed to make a comparison for egg (Table II). In this case raw and cooked whole egg were similar by using the GLRT and ED comparisons. However, raw egg white was significantly different by using the GLRT, and a much lower ED₀₅ value was calculated by comparison with either raw or cooked whole egg. Because the ED value is based on egg protein, egg white would contain a higher proportion of egg allergens by comparison with egg yolk or whole egg, which likely explains the difference. Although some patients with egg allergy are known to tolerate baked egg while still reacting to less well-cooked or raw egg,^{27,57-59} no differences were noted here between raw and cooked whole egg. Although raw and baked egg are not likely equivalent, the panel decided to consider them equivalent in this assessment while acknowledging the drawbacks of doing so.

DISCUSSION

The VITAL Expert Panel proposed reference doses based on dose-distribution modeling that ranged from 0.03 mg for egg protein to 10 mg for shrimp protein. Because the reference doses are based on the ED₀₁ value (or the 95% lower CI of the ED₀₅

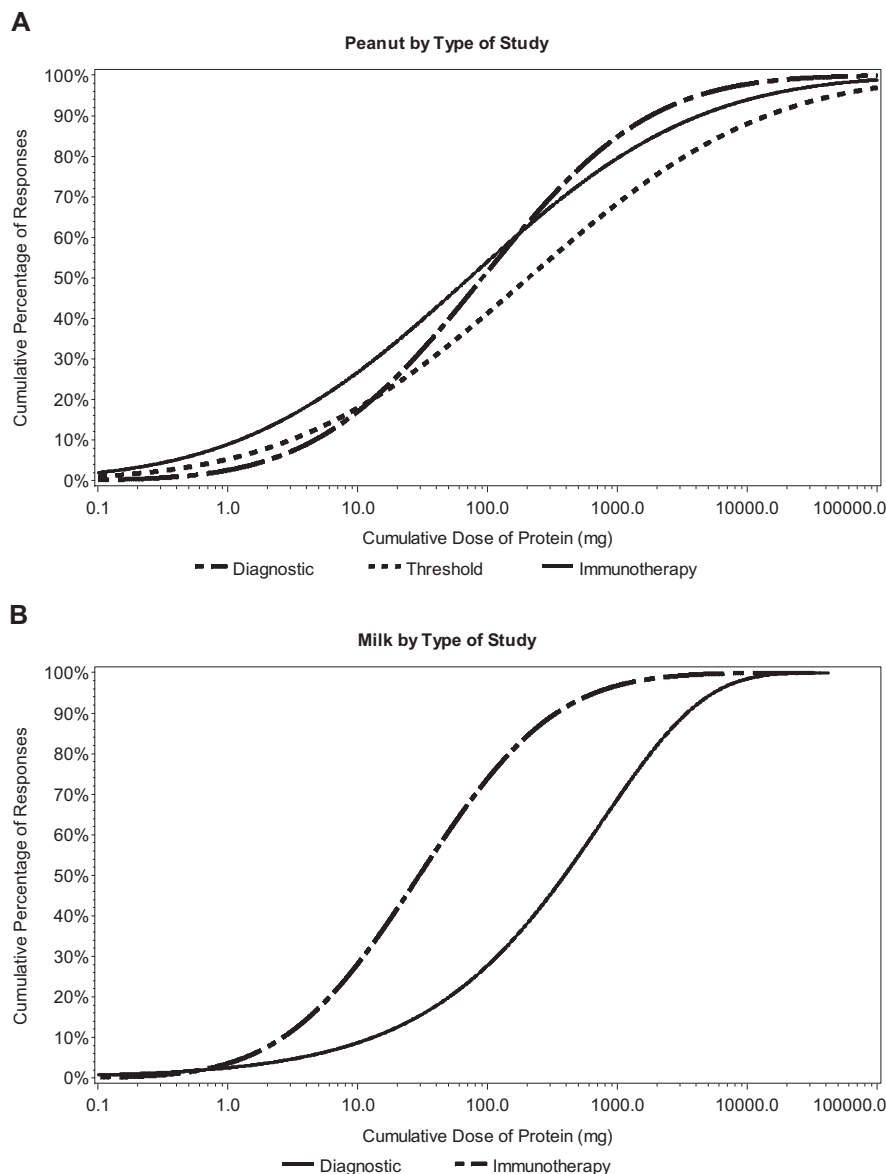


FIG 1. Dose-distribution models for individual thresholds (expressed as milligrams of protein) based on allergic patients for diagnostic studies, threshold studies, and immunotherapy studies: **A**, peanut; **B**, milk.

value for the less common foods), these doses would provide a level of protection of 99% for the allergic population represented in various challenges. The dose-distribution models predict that only 1% of the allergic population would not be fully protected when consuming foods with the reference dose of a particular allergen.

A similar situation exists for hypoallergenic infant formula, in which oral challenge trials of a much smaller number (typically 28-30) of infants with milk allergy establish that the particular formula is safe for 90% of such infants at a 95% confidence level.^{60,61} As expected, a small number of infants with milk allergy experience allergic reactions to hypoallergenic infant formula.^{62,63} These highly sensitive infants must receive more clinical counseling and alternative dietary strategies. Similarly, the small fraction of the allergic population that would not be fully protected at the reference dose must be identified and receive more intensive education about avoidance strategies. This

concern is balanced by the predicted improvement in the quality of life of the majority of the allergic population, who would have access to a wider variety of foods if the reference dose concept were adopted by the food industry and used to guide labeling decisions.

One limitation of these findings is that our derived reference doses are based on controlled clinical challenge trials that might differ in several important respects from community exposures experienced by patients with food allergy. Although community-based allergic reactions can occasionally be quite severe, one of the biggest factors is likely to be the size of the exposure dose, which could be quite large in some circumstances. However, clinical challenges are also controlled with respect to other factors that might influence reactivity, such as overall health status, medications, exercise, and others. The existence of such factors might argue for the application of additional uncertainty factors beyond the reference dose. Although the panel did not advocate

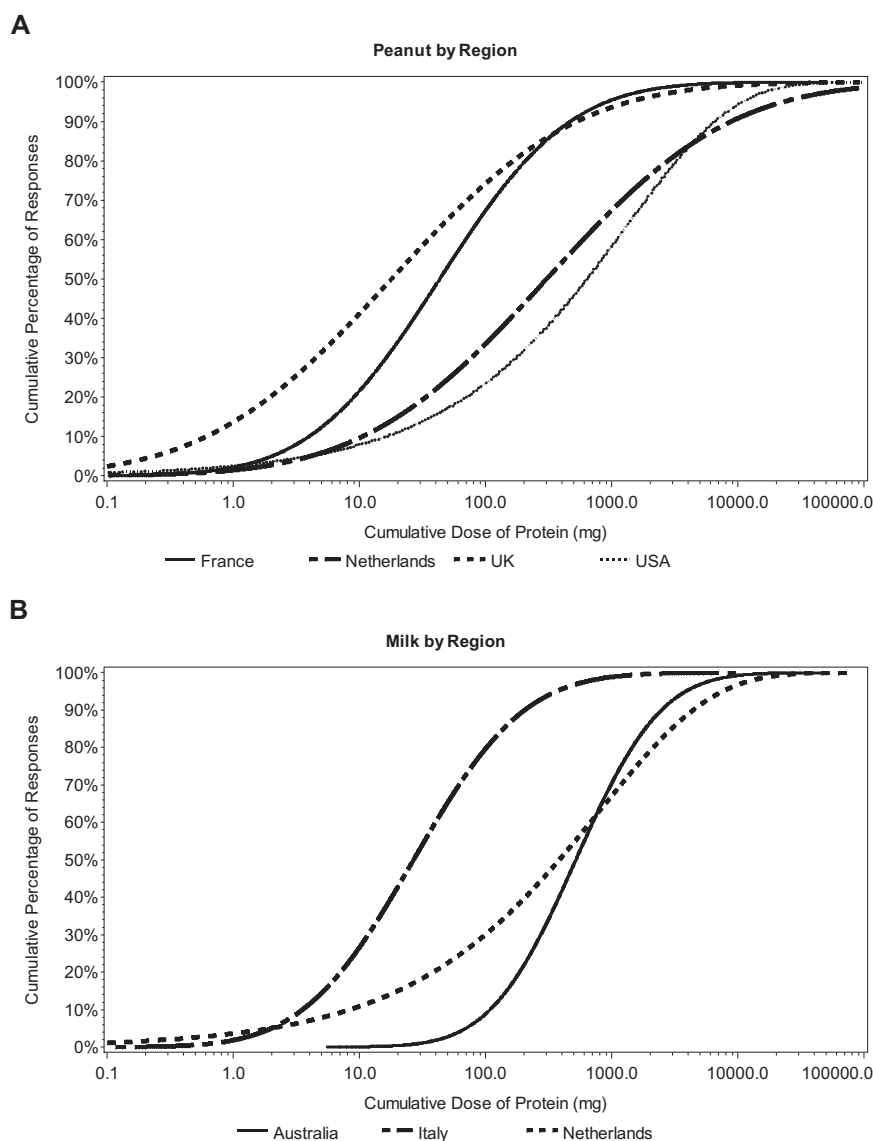


FIG 2. Dose-distribution models for individual thresholds (expressed as milligrams of protein) based on geographic location: **A**, peanut; **B**, milk.

the use of uncertainty factors, patients should certainly be counseled to be more careful about avoidance diets during times of ill health or vigorous exercise. Patients with suboptimal medication status are likely at greater risk, but the focus should be to improve their access to appropriate treatment rather than adjusting reference doses.

Of course, the dose selected as the reference dose influences not only the proportion of allergic patients reacting but also the severity of that reaction. Although the reference doses would be predicted to elicit no reaction in 99% of the allergic population, they would likely provoke mostly mild allergic reactions in the remainder of the patients, as previously documented for 286 patients with peanut allergy in a diagnostic series from Nancy, France.¹⁸ In contrast, Perry et al⁶⁴ documented that 28% of patients experienced severe symptoms during diagnostic challenges at the initial dose when considerably higher doses were used. Similarly, Sicherer et al⁶⁵ reported that up to 20% of patients experienced severe symptoms during diagnostic challenges at initial

doses of 400 to 500 mg with milk, peanut, egg, and wheat but not with soy or fish. Published studies that began oral challenges at doses of 400 to 500 mg of the allergenic food were not used in the curated threshold database because the first interval dose was quite large, which would have increased the uncertainty around the low-dose estimates of the ED₀₁ and ED₀₅ values of interest.¹⁵ The reference dose for peanut is 25 times lower than the lowest dose that Wainstein et al²⁸ reported as leading to anaphylaxis.

The recent study of Rolinck-Werninghaus et al⁶⁶ with patients allergic to egg, milk, wheat, or soy also provides evidence for a lower proportion of severe reactions at lower doses. Thus although reference doses are meant to protect the vast majority of allergic consumers against any reaction, it is reasonable to conclude that they are also likely protect most, if not all, of the highly reactive patients against severe reactions. Further clinical research on low-dose oral challenges with a wider range of foods is needed to provide a firmer basis for this observation. The

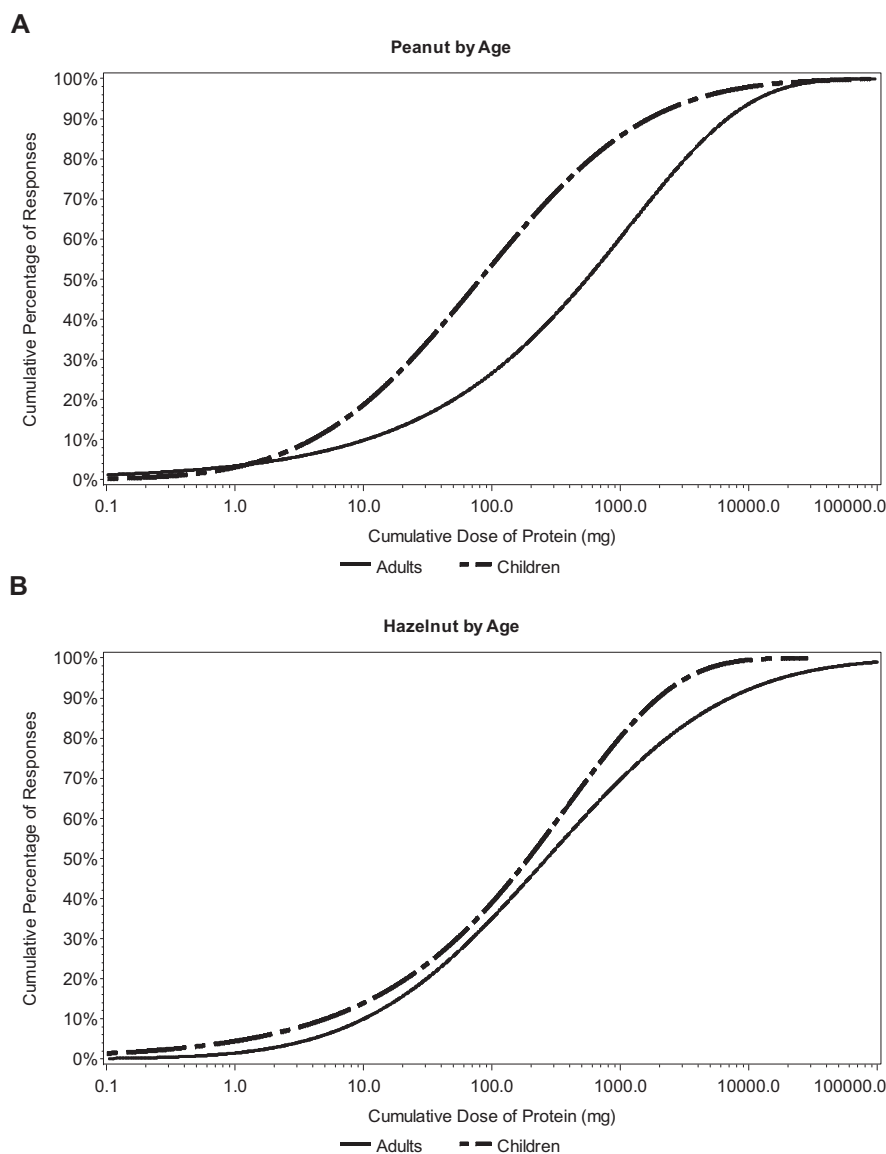


FIG 3. Probability distribution models for individual thresholds (expressed as milligrams of protein) based on age of the allergic patient at challenge: **A**, peanut; **B**, hazelnut.

comparative safety of the reference doses in terms of the low likelihood that such doses might provoke severe reactions if adopted by the food industry for labeling purposes could alleviate the anxiety that many patients with food allergies experience with respect to selection of packaged foods.^{67,68}

Precautionary labeling has arguably lost its value to the consumer with food allergy because its use cannot presently be associated with any specific level of risk. Evidence indicates that some allergic consumers are ignoring such statements.⁶ If reference doses are established and can be used to effectively guide labeling decisions, then the presence of a precautionary labeling statement would be tied to a specific level of risk. More importantly, the absence of a precautionary label statement would indicate that the product is safe for 99% of consumers with food allergy. Clinically, the individual threshold doses of patients with food allergy are not often determined. However, with the establishment of reference doses and associated labeling guidance,

the identification of the most sensitive patients with food allergy (the remaining 1%) would be important because these patients would benefit from additional dietary counseling. That might be accomplished by administering a single dose (eg, the ED₀₅) of the appropriate food to patients during clinical diagnosis to identify the most sensitive patients.

The proliferation of precautionary labeling and its adverse effect on patients with food allergy is increasingly recognized in the clinical community.^{69,70} The current status of precautionary labeling has also led to confusion in the clinical community and therefore inconsistent advice delivered to patients.⁷⁰ Precautionary labeling abounds because it is voluntary and neither the food industry nor any public health agency has established boundaries on its use. The establishment of science-based reference doses would allow the food industry, public health agencies, or both to develop limits on the use of precautionary labeling. Harmonized action levels, if used by the food industry, will benefit

TABLE II. Estimated EDs for peanut, milk, and egg as affected by the nature of the dose material

Allergen	Dose material	ED ₀₅ (95% CI)*
Peanut	Pulverized peanut ²⁸⁻³¹	2.1 (1.5-2.9)
Peanut	Peanut flour ^{24,33-40,†‡}	1.4 (0.9-2.2)
Milk	Liquid cow's milk ^{24,25,41-51§}	1.9 (1.1-3.1)
Milk	Nonfat dry milk ⁵²⁻⁵⁵	2.7 (0.7-10.4)
Egg	Cooked whole egg ^{24,27,49,56‡}	4.9 (2.1-11.5)
Egg	Raw whole egg ^{26,29,51,56}	3.4 (0.6-20.1)
Egg	Raw egg white ^{46,47}	0.2 (0.05-0.6)

*All ED values are expressed in terms of milligrams of protein from the respective allergenic source.

†WKZ: Wilhelmina Children's Hospital of the University Medical Center Utrecht, Utrecht, The Netherlands.

‡UMCU: University Medical Center Utrecht, Utrecht, The Netherlands.

§JBZ: Jeroen Bosch Hospital, The Netherlands.

allergic consumers. Action levels would establish sound science-based levels of protection that could be readily communicated to different stakeholders.

For the establishment of reference doses and their use for associated guidance on precautionary labeling to be most meaningful, the absence of a precautionary statement must also be tied to some form of positive indication on the package label to indicate that the product has been evaluated in terms of the reference dose. Consumption levels must also be considered to determine whether a food contains a dose of the allergenic food above the reference dose. At any particular concentration of allergen residue, the risk of an allergic reaction will be higher for a food that is typically consumed in large amounts as opposed to a food that is eaten in much smaller amounts, such as a condiment or a garnish.

In conclusion, the establishment of science-based reference doses for the VITAL program in Australia as presented here is likely to enhance its credibility and might reduce the extent of precautionary labeling, resulting in more meaningful food choices for the allergic consumer. The recommended reference doses are without exception less conservative than the action levels used in the 2007 VITAL program, thus making application of the new reference doses both achievable and verifiable. We anticipate that VITAL 2.0 is likely to garner international support from the manufacturing industry. If uptake by industry is high, there is likely to be a profound effect on both the reliability and increased dietary choices for allergic consumers. This would not only enable allergic consumers to more safely make food choices but at the same time choose from a significantly wider variety of manufactured foods.

A collaborative effort was formed between the Allergen Bureau of Australia and the FARRP of the University of Nebraska (United States), with support from TNO (The Netherlands) and Unilever (United Kingdom), to allow the establishment of a scientific expert panel to review risk assessment approaches and make recommendations relative to the action levels contained in the VITAL grid (food allergen concentration levels that trigger recommendations for precautionary labeling). The scientific expert panel only provided recommendations on the grid, leaving all other aspects of the VITAL program to the Allergen Bureau. Members of the panel were Steve Taylor (FARRP, chair of Panel), Joseph Baumert (FARRP), Rene Crevel (Unilever), Geert Houben (TNO), Simon Brooke-Taylor (Australia Allergen Bureau consultant), and Katrina (Katie) Allen (Pediatric Gastroenterologist/Allergist, Australia). During the process, the panel received considerable assistance from Ben

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Key messages

- We have established reference doses for 11 commonly allergenic foods to guide a rational approach by manufacturers for precautionary labeling of foods.
- The new reference doses based on EDs for 1% of the allergic population were estimated as the following: peanut, 0.2 mg of protein; cow's milk, 0.1 mg; egg, 0.03 mg; and hazelnut, 0.1 mg.
- These new levels will enable manufacturers to apply credible precautionary labeling and provide increased consumer confidence in their validity and reliability.

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1 **Online repository Table 1. Number and Sources of Threshold Data Gleaned From Publications and Unpublished Clinical**
 2 **Records**

Allergen	Study	Total No. with Objective Symptoms	Right Censored ^a	Left Censored ^b	Adults	Children	Age Uncertain
Peanut							
Published	Atkins et al. ¹	2	0	0	2	0	0
	Hourihane et al. ²	13	11	0	10	3	0
	Wensing et al. ³	26	20	0	24	2	0
	Lewis et al. ⁴	40	0	3	0	0	40
	Flinterman et al. ⁵	22	11	0	0	22	0
	Leung et al. ⁶	23	8	1	0	0	23
	Oppenheimer et al. ⁷	4	0	0	1	0	3
	Nelson et al. ⁸	12	0	1	12	0	0
	Nancy ^{9,c}	283	10	7	7	275	1
	Anagnostou et al. ¹⁰	18	0	7	1	17	0
	Clark et al. ^{11,12}	5	0	1	0	5	0
	Nicolaou et al. ¹³	10	0	2	0	10	0
	Blumchen et al. ¹⁴	22	0	2	0	22	0
	Wainstein et al. ¹⁵	8	0	0	0	8	0

	Patriarca et al. ¹⁶	1	0	0	1	0	0
	Blom et al. ¹⁷	135	50	5	0	135	0
Unpublished	WKZ ^d	85	5	1	0	85	0
	UMCU ^{e,f}	41	17	0	41	0	0
Total		750	132	30	99	584	67
Milk							
Published	Blom et al. ¹⁷	93	13	7	0	93	0
	Staden et al. ¹⁸	3	0	0	0	3	0
	Norgaard and Bindslev-Jensen ¹⁹	3	0	1	3	0	0
	Morisset et al. ²⁰	3	0	1	0	0	3
	Caminiti et al. ²¹	11	0	0	0	11	0
	Patriarca et al. ²²	8	0	0	0	8	0
	Morisset et al. ²³	11	0	1	0	11	0
	Longo et al. ²⁴	60	0	9	0	60	0
	Skripak et al. ²⁵	20	0	14	0	20	0
	Lam et al. ²⁶	8	2	0	7	1	0
	Hill et al. ²⁷	53	0	11	0	53	0

	Fiocchi et al. ²⁸	12	0	5	0	12	0
	Baehler et al. ²⁹	10	0	0	0	10	0
	Flinterman et al. ³⁰	11	0	3	0	11	0
	Orhan et al. ³¹	4	0	0	0	4	0
	Devenney et al. ³²	2	0	1	0	2	0
	Host et al. ³³	3	0	2	0	3	0
	Dambacher et al. ⁵⁸	21	0	3	0	21	0
Unpublished	UMCU ^e	15	4	1	15	0	0
Total		351	19	59	25	323	3
Egg							
Published	Staden et al. ¹⁸	3	0	1	0	3	0
	Benhamou et al. ³⁴	33	0	9	0	33	0
	Morisset et al. ²⁰	20	0	4	0	0	20
	Caffarelli et al. ³⁵	13	0	0	0	13	0
	Morisset et al. ²³	15	0	0	0	15	0
	Atkins et al. ¹	1	0	0	1	0	0
	Norgaard and Bindselev-Jensen ¹⁹	7	0	0	6	1	0
	Knight et al. ³⁶	7	0	5	0	7	0
	Unsel et al. ³⁷	1	0	0	1	0	0

	Orhan et al. ³¹	3	0	0	0	3	0
	Eggesbo et al. ³⁸	7	0	1	0	7	0
	Blom et al. ¹⁷	53	13	2	0	53	0
							0
Unpublished	FARRP ^h	40	19	1	1	39	0
	UMCU ^e	3	1	1	3	0	0
Total		206	33	24	12	174	20
Hazelnut							
Published	Wensing et al. ³⁹	29	27	1	29	0	0
	Blom et al. ¹⁷	28	11	2	0	28	0
Unpublished	UMCU ^{e,i}	30	15	0	30	0	0
	UBer ^j	82	10	1	82	0	0
	WKZ ^d	33	4	0	0	33	0
Total		202	67	4	141	61	0
Soybean							
Published	Ballmer-Weber et al. ⁴⁰	22	11	0	0	0	22
	Zeiger et al. ⁴¹	9	0	0	0	9	0
	Magnolfi et al. ⁴²	5	1	2	0	5	0

	Fiocchi et al. ²⁸	7	0	1	0	7	0
	Blom et al. ¹⁷	10	7	1	0	10	0
Unpublished	FARRP ^h	8	3	0	6	2	0
	UBer ^j	17	4	2	17	0	0
	UMCU ^e	2	2	0	2	0	0
Total		80	28	6	25	33	22
Wheat							
Published	Ito et al. ⁴³	21	0	1	0	21	0
	Pastorello et al. ⁴⁴	3	1	1	0	3	0
	Scibilia et al. ⁴⁵	13	0	3	12	1	0
Unpublished	UMCG ^g	3	0	0	0	3	0
Total		40	1	5	12	28	0
Cashew							
Published	Blom et al. ¹⁷	31	16	1	0	31	0
Total		31	16	1	0	31	0
Mustard							
Published	Figuerola et al. ⁴⁶	14	10	0	9	5	0

	Morisset et al. ⁴⁷	4	0	0	0	4	0
	Rance et al. ⁴⁸	15	0	2	0	15	0
Total		33	10	2	9	24	0
Lupine							
Published	Moneret-Vautrin et al. ⁴⁹	5	0	0	0	5	0
	Fiocchi et al. ⁵⁰	2	0	1	0	2	0
	Shaw et al. ⁵¹	2	0	0	0	2	0
Unpublished	UMCU ^e	15	7	1	15	0	0
Total		24	7	2	15	9	0
Sesame Seed							
Published	Leduc et al. ⁵²	12	0	1	7	5	0
	Morisset et al. ²⁰	1	0	0	0	0	1
	Kolopp-Sarda et al. ⁵³	1	0	0	0	0	1
	Kanny et al. ⁵⁴	7	1	1	6	1	0
Total		21	1	2	13	6	2
Shrimp							
Published	Atkins et al. ¹	4	0	0	4	0	0
	Daul et al. ⁵⁵	21	12	0	21	0	0

Unpublished	FARRP^h	23	14	0	23	0	0
Total		48	26	0	48	0	0

^a Number of right-censored subjects (NOAEL = highest challenge dose; LOAEL set to infinity)

^b Number of left-censored subjects (NOAEL set to zero; LOAEL = lowest challenge dose)

^c Published only in summarized form

^d WKZ –Wilhelmina Children’s Hospital of the University Medical Center Utrecht, The Netherlands

^e UMCU – University Medical Center Utrecht, The Netherlands

^f Includes Peeters et al. ⁵⁶

^g UMCG – University Medical Center Groningen, The Netherlands

^h FARRP – Food Allergy Research & Resource Program, University of Nebraska – Lincoln, U.S.

ⁱ Includes Flinterman et al. ⁵⁷

^j Universitätsmedizin Berlin, Germany

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7 **Online repository Table 2. Conversion Factors Used to Normalize the Threshold Challenge Material.**

Allergen	Conversion to:	Protein Content	mg Protein	mg Food	Reference
Peanut	Whole Peanut	25.0%	1	4.0	Taylor et al. ¹ assumptions
Peanut	Defatted Peanut Flour	50.0%	1	2.0	Taylor et al. ¹ assumptions
Milk	Liquid Milk	3.3%	1	30.3	USDA - 2% Milk
Milk	NFDM	35.1%	1	2.8	USDA - Instant NFDM
Egg	Raw Whole Egg	12.6%	1	8.0	USDA
Egg	Raw Egg White	10.5%	1	9.5	NEVO
Egg	Cooked Whole Egg	12.6%	1	7.9	USDA
Egg	Cooked Egg White	10.5%	1	9.5	NEVO
Egg	Dried Whole Egg	46.0%	1	2.2	NEVO
Egg	Dried Egg White	81.1%	1	1.2	USDA
Hazelnut	Hazelnut Flour	15.7%	1	6.4	In Wensing et al. ²
Soy	Whole Soybean	40.0%	1	2.5	Assumptions made by working group
Soy	Soy Flour	53.0%	1	1.9	In Ballmer-Weber et al. ³

Soy	Soy Milk	3.6%	1	27.8	provided by UMCU
Wheat	Raw or Cooked Wheat Flour	10.0%	1	10.0	NEVO and USDA
Cashew	Cashew Flour	19.0%	1	5.3	NEVO
Mustard	Mustard Seed	26.1%	1	3.8	USDA - S. alba seed
Lupin	Lupin Flour	36.2%	1	2.8	USDA
Lupin	Yellow Lupin Flour	40.0%	1	2.5	In Shaw et al. ⁴
Sesame	Crushed Sesame Seeds	17.0%	1	5.9	USDA - Roasted Seed
Sesame	Sesame Seed Flour	30.8%	1	3.2	USDA - High Fat Flour
Shrimp	Whole Cooked Shrimp	22.8%	1	4.4	USDA - Steamed/Boiled
Celery	Raw Celery Root	2.0%	1	50.0	NEVO
Fish	Snapper	26.3%	1	3.8	USDA
Fish	Cooked Codfish	23.0%	1	4.3	NEVO
Fish	Raw Codfish	18.3%	1	5.5	NEVO
Fish	Catfish	18.4%	1	5.4	USDA
Fish	Halibut	19.4%	1	5.2	NEVO
Fish	Tuna	23.7%	1	4.2	provided by UMCU
Fish	Tilapia	17.8%	1	5.6	provided by UMCU

USDA, USDA National Nutrient Database; NEVO, The Dutch Food Composition Table; UMCU, University Medical Center Utrecht.

The protein levels listed in Table 1 are general guidelines for the values used to convert from protein to whole food. In many cases (e.g. soy milk, hazelnut flour, wheat flour), numerous protein levels were available from multiple centers and used to convert their respective DBPCFC values to mg protein. In these instances, a representative protein value was chosen for the table and listed with its source.

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