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# Summary of the VITAL Scientific Expert Panel Recommendations





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### **Important Notice (25 October 2011)**

The information provided in this summary is for information purposes only and is not complete and should not be relied upon to conduct any part of an allergen risk assessment. The updated VITAL 2.0 program will allow you to use the updated information in order to determine if a precautionary labelling statement is required by guiding you through the important steps when undertaking a thorough allergen risk assessment. For information about VITAL 2.0 you can attend an information session during November 2011, or see the Allergen Bureau website for more details.

# Summary of the VITAL Scientific Expert Panel Recommendations

## The Expert Panel and Purpose

The VITAL Scientific Expert Panel (The Panel) was formed in collaboration between the Allergen Bureau (Australia & New Zealand), the Food Allergy Research & Resource Program (FARRP) of the University of Nebraska (USA) & the Netherlands Organization for Applied Scientific Research (TNO) to make recommendations for the Action Levels in the VITAL grid. Members of the Panel were Steve Taylor (FARRP, chair of Panel), Joseph Baumert (FARRP), Rene Crevel (Unilever), Geert Houben (TNO), Simon Brooke-Taylor (Allergen Bureau consultant), and Katie Allen (Paediatric Allergist, Australia). The Panel was assisted by Ben Remington (FARRP), Astrid Kruizinga (TNO), Ellen Dutman (TNO), and Harrie Buist (TNO).

The Panel met initially in Sydney in January 2011 and thereafter worked out of session. The Panel identified that sufficient new clinical oral challenge threshold data now existed (from published literature, unpublished clinical records in the Netherlands and Germany and partially completed FARRP studies), for the major allergens of concern, to allow the development of dose distribution relationships using statistical modeling as described by Crevel et al (2007)<sup>1</sup>. The derived dose response curves enable the identification of an eliciting dose of an allergen (ED<sub>p</sub>) at which a proportion of the allergic population (p) would be likely to react, but, does not identify a dose below which no allergic individual would react.

Action Levels in the original VITAL grid were expressed as concentrations with a 5g serving size. The Panel recommended that Action Levels in the revised VITAL grid should address the use of different reference amount / serving size appropriate to consumption patterns for individual foods. Consequently, an interactive VITAL grid is proposed that will calculate the Action Level concentrations (ppm), from the Reference Dose (mg allergen protein) recommended by the Panel and a Reference Amount / Serving Size specific to the food, inputted by the user. The choice of Reference Amount / Serving Size can significantly affect the Action Level concentration and hence the level of risk for sensitive consumers. The Panel, therefore, recommends that this Reference Amount / Serving Size be determined by the use of dietary consumption data. This should include, for each specific product type & where available, appropriate national dietary surveys (either from Australian and New Zealand sources or from other countries with similar dietary patterns) or internal company data, including mean consumption and the 95th percentile consumption.

<sup>1</sup> For each subject, the NOAEL and LOAEL for mild objective responses were recorded as mg of total allergen protein. The true threshold dose lies, by definition, between the NOAEL and LOAEL doses. Individual data were analyzed using Interval-Censoring Survival Analysis and fitted to the parametric models using the SAS LIFEREG procedure (SAS v9.1) described by Taylor et al. (2009). Individuals reacting to the first challenge dose were treated as left-censored, while individuals failing to respond to the uppermost challenge dose were treated as right-censored.

# Results

The distributions for individual subject thresholds, for both discrete and cumulative doses<sup>2</sup>, were modelled separately for each allergenic food, using three statistical models (log normal, log logistic, and Weibull). The eliciting doses for all three models were determined, with preference being given to the model with the best fit at low doses, as determined by statistical and visual examination. Where sufficient data existed, in addition to the combined data, distributions were modeled separately for infants and children versus adults. The challenge doses were normalized in all cases to mg of protein from the allergenic food.

Data from large numbers of subjects were available for peanut, milk, egg, and hazelnut. Smaller amounts of individual threshold data were found for soybean, wheat, cashew, mustard, lupin, sesame seed, shrimp, celery and fish.

## **Peanut**

Peanut thresholds were obtained for 750 individuals (489 published and 261 unpublished), comprising: 584 children, 99 adults, and 67 of undetermined age; 30 left-censored and 132 right-censored. The peanut data set was considered to be excellent.

The Panel recommends that the Reference Dose be set at 0.2 mg peanut protein, based on the ED01 values of the log normal and log logistic distributions based on discrete and cumulative doses for both adults and children at (Table 1).

## **Milk**

Milk thresholds were obtained for 351 individuals (222 published studies and another 129 unpublished), comprising: 323 children, 25 adults and 3 of undetermined age; 59 left-censored and 19 right-censored. Overall, the milk data set was considered to be excellent.

The Panel recommends that the Reference Dose be set at 0.1 mg milk protein, based on the ED01 values of the log normal and log logistic distributions based on discrete and cumulative doses for both adults and children (Table 1).

## **Egg**

Egg thresholds were obtained for 206 individuals (110 published and 96 unpublished), comprising: 174 children, 12 adults, and 20 of undetermined age; 24 left-censored and 33 right-censored. Overall, the egg data set was considered to be excellent. The data set pooled data for both raw and cooked eggs.

The Panel recommends that the Reference Dose be set at 0.03 mg egg protein consistent with the ED01 and 95% lower confidence interval of the ED05 values of the Weibull and other distributions and based on discrete and cumulative doses for children (Table 1).

<sup>2</sup> While use of the discrete dose is the most conservative choice for risk assessment purposes, little difference existed between the ED values at the lower portion of the distribution curves or the overall curve fits.

## Hazelnut

Hazelnut thresholds were obtained for 202 individuals (29 published and 173 unpublished), comprising: 61 children and 141 adults; 4 left-censored and 67 right-censored. Overall, the hazelnut data set was considered to be good but would be enhanced by publication of the unpublished data.

The Panel recommends that the Reference Dose be set at 0.1 mg hazelnut protein, based on the ED01 and 95% lower confidence interval of the ED05 values of the log logistic and other distributions and also on discrete and cumulative doses for adults and children (Table 1).

## Soybean

Individual soybean thresholds were obtained for 80 individuals (43 individuals published and 37 unpublished), comprising: 33 children, 25 adults, and 22 of undetermined age; 6 left-censored and 28 right-censored. Overall, the soybean data set was considered to be sufficient. The Panel observed that some challenge studies with soy flour indicate reasonably high individual soybean thresholds, whereas studies using soy milk with subjects selected on the basis of a history of adverse reactions to a particular brand(s) of soy milk appear to have indicate lower individual thresholds.

The Panel recommends that the Reference Dose be set at 1.0 mg soybean protein, consistent with the 95% lower confidence interval of the ED05 values of the log normal and other distributions based on discrete and cumulative doses for children and adults having soy flour challenges (Table 1). The Panel noted that this level may not completely protect certain individuals sensitive to soy milk.

## Wheat

Individual wheat thresholds were obtained for 40 individuals<sup>3</sup> (37 published and 3 unpublished), comprising: 28 children and 12 adults; 5 left-censored and 1 right-censored. Overall, the wheat data set was considered to be sufficient.

The Panel recommends that the Reference Dose be set at 1.0 mg wheat protein, consistent with the 95% lower confidence interval of the ED05 values of all three distributions based on discrete and cumulative doses for adults and children (Table 1). The Panel noted that wheat-allergic consumers would be largely protected by foods containing <20 ppm gluten.

## Cashew

Cashew thresholds were obtained for 31 children (all unpublished); 1 left-censored and 16 right-censored. Overall, the data set was considered to be marginally sufficient.

The Panel recommends that a provisional Reference Dose only be set at 2.0 mg cashew protein, consistent with the 95% lower confidence interval of the ED05 values of all three distributions based on discrete and cumulative doses for children (Table 1).

## Mustard<sup>4</sup>

Mustard thresholds were obtained for 33 individuals (all published), comprising: 9 children, 9 adults, and 15 of undetermined age; 2 left-censored and 10 right-censored. Overall, the data set was considered as sufficient.

<sup>3</sup> with confirmed IgE-mediated allergic reactions to wheat

<sup>4</sup> Priority allergen in the EU and Canada.

## Mustard (continued)

The Panel recommends that the Reference Dose be set at 0.05 mg mustard protein, consistent with the 95% lower confidence interval of the ED05 values of all three distributions based on discrete and cumulative doses for children and adults (Table 1).

## Lupin<sup>5</sup>

Lupin thresholds were obtained for 24 individuals (9 published and 15 unpublished). Comprising: 9 children and 15 adults; 2 left-censored and 7 right-censored. Overall, the data set was considered as sufficient.

The Panel recommends that the Reference Dose be set at 4.0 mg lupin protein, consistent with the 95% lower confidence interval of the ED05 values of the log normal and log logistic distributions based on discrete and cumulative doses for children and adults (Table 1).

## Sesame seed

Sesame seed thresholds were obtained for 21 individuals (all published), comprising: 6 children, 13 adults, and 2 of undetermined age.; 2 left-censored and 1 right-censored. Overall, the sesame seed data set was considered as marginally sufficient.

The Panel recommends that the Reference Dose be set at 0.2 mg sesame seed protein, consistent with the 95% lower confidence interval of the ED05 values of the three distributions based on discrete and cumulative doses for children and adults (Table 1).

## Shrimp

Shrimp<sup>6</sup> thresholds were obtained for 48 adults (25 published and 23 unpublished) ; 26 right-censored and none left-censored. Overall, the shrimp data set was considered as marginally sufficient.

The Panel recommends that the Reference Dose be set at 10 mg shrimp protein, consistent with the 95% lower confidence interval of the ED05 values of the three distributions based on discrete and cumulative doses for adults (Table 1).

## Celery<sup>7</sup>

Celery thresholds were obtained for 39 individuals (12 published and 27 unpublished), comprising: 27 adults and 12 of undetermined age; 15 left-censored and 4 right-censored. The celery data set was considered as insufficient to allow an estimate of ED values.

## Fish

Fish thresholds were obtained for 19 individuals (15 published and 4 unpublished), comprising: 18 adults and 1 child; 6 left-censored and 2 right-censored. The data set covered challenges with several different fish species, including cod (10), catfish (5), snapper (1), halibut (1), tuna (1), and tilapia (1). The fish data set was considered as insufficient to allow an estimate of ED values.

## Other Tree Nuts

The Panel was unable to locate sufficient data on individual thresholds for any other tree nuts, including walnut, pecan, almond, pistachio, brazil nut, macadamia nut, pine nut.

<sup>5</sup> Priority allergen in the EU.

<sup>6</sup> While crustacea is a priority allergen in the ANZ Code individual threshold data exist only for shrimp.

<sup>7</sup> Priority allergen in the EU.<sup>7</sup> Priority allergen in the EU.<sup>5</sup>

# References

Crevel RWR, Briggs D, Hefle SL, Knulst AC, Taylor SL. Hazard characterization in food allergen risk assessment: the application of statistical approaches and the use of clinical data.. Food ChemToxicol 2007;45:691–701.

Taylor SL, Crevel RWR, Sheffield D, Kabourek J, and Baumert J. 2009. Threshold dose for peanut: a risk assessment based upon published results from challenges of peanut-allergic individuals. Food Chem. Toxicol. 47:1198-1204.

**Table 1. Summary of VITAL Scientific Expert Panel Recommendations.**

Allergen	mg Protein Level	Quantitative Risk	Quality of database
<b>Peanut</b>	0.2	ED01	Excellent
<b>Milk</b>	0.1	ED01	Excellent
<b>Egg</b>	0.03	ED01 and ED05 95% lci*	Excellent
<b>Hazelnut</b>	0.1	ED01 and ED05 95% lci	Good
<b>Soy</b>	1.0	ED05 95% lci Note: this level may not completely protect certain individuals sensitive to soy milk.	Sufficient
<b>Wheat</b>	1.0	ED05 95% lci Note; wheat-allergic consumers would be largely protected by foods containing <20 ppm gluten	Sufficient
<b>Cashew</b>	2.0 (provisional)	ED05 95% lci	Marginally Sufficient
<b>Mustard</b>	0.05	ED05 95% lci	Sufficient
<b>Lupin</b>	4.0	ED05 95% lci	Sufficient
<b>Sesame</b>	0.2	ED05 95% lci	Marginally Sufficient
<b>Shrimp</b>	10	ED05 95% lci	Marginally Sufficient
<b>Celery</b>	n/a		Insufficient
<b>Fish</b>	n/a		Insufficient
<b>Other tree nuts</b> (walnut, pecan, almond, pistachio, brazil nut, macadamia nut, pine nut)			Insufficient

\* Lower Confidence Interval

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