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Summary of the 2019 VITAL Scientific Expert Panel Recommendations

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The Expert Panel and Purpose

The VITAL Scientific Expert Panel (The Panel) was formed in 2011 to make recommendations for the Reference Doses in the VITAL Program. The Panel is a 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 VITAL Program as necessary.

This document is a summary of the recommendations for an updated set of Reference Doses determined in the most recent meetings of the Panel (in Copenhagen, October 2018 and by teleconference, April 2019). The new set of Reference Dose recommendations are referred to as "VITAL 3.0" and supersede the VITAL 2.0 Reference Dose recommendations released in 2011.

Members of The Panel present at the 2018 and 2019 meetings were:

- Steve Taylor (FARRP, chair of Panel),
- Joseph Baumert (FARRP),
- Rene Crevel (FARRP/independent consultant, formerly Unilever),
- Geert Houben (TNO),
- Simon Brooke-Taylor (Allergen Bureau) and;
- Ben Remington[1] (TNO).

Marty Blom (TNO) also participated as an advisor and Kirsten Grinter (Allergen Bureau) attended as an observer.

Methods

Allergen Threshold Modelling

The previous Reference Dose recommendations (VITAL 2.0) used 3 discrete models (i.e. Weibull, Log Logistic and Log Normal) and Eliciting Doses (ED_p) were identified by "expert judgement" of the best fit from the 3 models in the relevant low dose section of the model.

The Eliciting Dose (ED), where EDp refers to the dose of total allergen protein that is predicted to produce a response in p% of the allergic population, represents the dose of an allergen (EDp) at which a proportion of the allergic population would be likely to react to but, importantly, does not identify a dose below which no allergic individual would react. Thus, the ED01 and ED05 are the doses at which only 1% and 5%, respectively, of the allergic population would react with objective symptoms.

The Panel was advised that ongoing collaboration between FARRP, TNO and Dr. Matthew Wheeler, US CDC [National Institute for Occupational Safety and Health (NIOSH)] to improve the allergen dose distribution modelling has resulted in the development a new Stacked Model Averaging program[2]. The program incorporates 5 different statistical models (Weibull, Log Logistic, Log Normal, Log Double Exponential, General Pareto) and produces a single "averaged" distribution.

The Panel agreed to adopt the Stacked Model Averaging program to determine dose distribution relationships for each allergenic food for their Reference Dose recommendations.

The Panel noted that the cumulative ED_{01} for peanut recommended in 2011 (0.2 mg peanut protein) and adopted as the Reference Dose into VITAL 2.0 was confirmed when the 2011 data set was remodelled using Stacked Model Averaging program.

The Stacked Model Averaging program produces a single curve for each allergen from which Eliciting Doses may be derived. The VSEP identified the ED_{01} and ED_{05} for each allergen. The Panel considered the more conservative estimate to be appropriate after fitting the data to both discrete and cumulative dosing schemes[3]. The Panel considered that ED_{01} better met the requirements of the Allergen Bureau which included: minimising the percentage of the allergic population at risk from cross contact allergens in unlabelled products; increasing the likelihood of global acceptance of VITAL; and a level of risk no greater than VITAL 2.0. Additionally, ED_{05} values are also provided for information (Table 2).

The Panel recommends the adoption of ED_{01} values as the Reference Doses for VITAL 3.0.

1.Ben Remington previously participated as an advisor to the VSEP.

2. Wheeler MW, Westerhout J, Baumert JL, Remington BC. Bayesian Stacked Parametric Survival with Frailty Components and Interval Censored Failure Times. August 2019. http://arxiv.org/abs/1908.11334.

3. Remington et al, in prep.

Results

Sufficient data were available for Egg, Hazelnut, Lupin, Milk, Mustard, Peanut, Sesame, Shrimp, Soy, Wheat, Cashew, Celery, Fish and Walnut. There was a significant increase in the number of individuals who had undergone challenge studies for most allergens and also, therefore, the number of data points available for dose distribution modelling (Table 1). As with the 2011 recommendations, all the data from adults were derived from Double Blind Placebo Controlled Food Challenges[4] (DBPCFCs), whereas blinding was not considered absolutely necessary in the case of data from infants and very young children on the basis of clinical opinion.

Table 1 - Allergen threshold database 2011 vs 2019

Allergen	Number of available individual challenge studies	
	2011	2019
Egg	206	431
Hazelnut	200	411
Lupin	24	25
Milk	344	450
Mustard	33	33
Peanut	744	1306
Sesame	21	40
Shrimp	48	75
Soy (milk + flour)	51	87
Wheat	40	99
Cashew	31	245
Celery	39	82
Fish	19	82
Walnut	~15	74

4. DBPCFCs involve challenging participants under controlled conditions with increasing doses of an allergen or a placebo at intervals until a response is observed or the maximum scheduled dose is reached while both participants and clinical personnel are blinded to the material administered. These DBPCFC are used to derive the threshold doses for objective allergic reaction that underlie the ED values presented in this report. Recently TNO and FARRP in collaboration with an international clinical author group proposed a harmonised framework for the interpretation of food challenge results.

Westerhout J, Baumert JL, Blom WM, Allen KJ, Ballmer-Weber B, Crevel RWR, Dubois AEJ, Fernández-Rivas M, Greenhawt MJ, O'B Hourihane J, Koplin JJ, Kruizinga AG, Le T-M, Sampson HA, Shreffler WG, Turner PJ, Taylor SL, Houben GF, Remington BC, Deriving individual threshold doses from clinical food challenge data for population risk assessment of food allergens,Journal of Allergy and Clinical Immunology (2019), doi: https://doi.org/10.1016/j.jaci.2019.07.046.

Allergens for which the Reference Dose is **unchanged**

Peanut

Peanut thresholds were available for 1306 individuals (compared to 744 in 2011). The Panel identified the ED_{01} and $ED0_5$ for peanut as 0.2mg and 2.1 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be maintained at 0.2 mg peanut protein, based on the ED_{01} value.

Hazelnut (and Tree Nut default)

In VITAL 2.0 the Reference Dose for all Tree Nuts was recommended based on hazelnut challenge data. At its current meeting, the Panel considered that there were sufficient data points to establish ED values for hazelnut, cashew and walnut (Table 2).

Hazelnut thresholds were available for 411 individuals (compared to 200 in 2011). The Panel identified the ED_{01} and ED_{05} for hazelnut as 0.1 mg and 3.5 mg hazelnut protein respectively (Table 2).

Based on the absence of any reports of adverse reactions to tree nuts labelled in accordance with VITAL 2.0, **the Panel recommends that the Reference Dose for tree nuts**, other than walnut, pecan, cashew and pistachio, **be maintained at 0.1mg protein**, based on the ED_{01} value for hazelnut.

Mustard

Mustard thresholds were available for 33 individuals (unchanged from 2011). The Panel identified the ED_{01} and ED_{05} for mustard as 0.05 mg and 0.4 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be maintained at 0.05 mg mustard protein, based on the ED_{01} value.

Allergens for which an **increased** Reference Dose is Recommended

Egg

Egg thresholds were available for 431 individuals (compared to 204 in 2011). The Panel identified the ED_{01} and ED_{05} for egg as 0.2mg and 2.3 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be increased from 0.03 to 0.2 mg egg protein, based on the ED_{01} value.

Milk

Milk thresholds were available for 450 individuals (compared to 344 in 2011). The Panel identified the ED_{01} and ED_{05} for milk as 0.2mg and 2.4 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be increased from 0.1 to 0.2 mg milk protein, based on the ED_{01} value.

Shrimp

Shrimp thresholds were available for 75 individuals (compared to 48 in 2011). The Panel identified the ED_{01} and ED_{05} for shrimp as 25mg and 280 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be increased from 10 to 25 mg shrimp protein, based on the ED_{01} value.

4. New, lower Reference Doses have been recommended for cashew & pistachio and for walnut & pecan. The hazelnut Reference Dose is retained as the default for all other Tree Nuts.

Allergens for which a **reduced** Reference Dose is Recommended

Lupin

Lupin thresholds were available for 25 individuals (compared to 24 in 2011). The Panel identified the ED_{01} and ED_{05} for lupin as 2.6 mg and 15.3 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be reduced from 4 to 2.6 mg lupin protein, based on the ED_{01} value.

Soybean

Soybean thresholds were available for 87 individuals (compared to 51 in 2011). In 2011, the Panel observed that some challenge studies with soy flour indicated 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 appeared to indicate lower individual thresholds. As a result, in 2011, the Reference Dose was recommended based on soy flour challenges only and the studies with soy milk were excluded due to the inconsistencies between the brands. The Panel noted at the time that this level may not completely protect certain individuals sensitive to soy milk. At its current meeting, the Panel identified the ED_{01} and ED_{05} for soy (flour & milk) as 0.5mg and 10 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be reduced from 1.0 to 0.5 mg soy protein, based on the ED01 value.

Wheat

Wheat thresholds were available for 99 individuals (compared to 40 in 2011). The Panel identified the ED_{01} and $ED0_{5}$ for wheat as 0.7 mg and 6.1 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be reduced from 1.0 to 0.7 mg wheat protein, based on the ED_{01} value.

Sesame

Sesame thresholds were available for 40 individuals (compared to 21 in 2011). The Panel identified the ED_{01} and ED_{05} for sesame as 0.1 mg and 2.7 mg protein respectively (Table 2).

The Panel recommends that the Reference Dose be reduced from 0.2 to 0.1 mg sesame protein, based on the ED_{01} value.

Allergens for which a **new** Reference Dose is Recommended

Cashew (and Pistachio)

At its current meeting, the Panel considered that there were sufficient data points to establish ED values for cashew (Table 2)[6].

Cashew thresholds were available for 245 individuals (compared to 35 in 2011). The Panel identified the ED_{01} and ED_{05} for cashew as 0.05mg and 0.8 mg cashew protein respectively (Table 2).

In recognition of the potential for cross-reactivity between cashew and pistachio, the **Panel recommends that a new Reference Dose of 0.05 mg be established for cashew and pistachio protein**, based on the ED_{01} value for cashew.

Celery

Celery thresholds were available for 82 individuals (compared to 39 in 2011). The Panel identified the ED_{01} and ED_{05} for celery as 0.05 mg and 1.3 mg protein respectively (Table 2).

The **Panel recommends a Reference Dose of 0.05 mg celery protein**, based on the ED_{01} value.

Fish (finfish)

Finfish thresholds were available for 82 individuals (compared to 19 in 2011). The Panel identified the ED_{01} and ED_{05} for finfish as 1.3 mg and 12.1 mg protein respectively (Table 2). The Panel did not recommend a Reference Dose in 2011 and the original Action Level [0.1mg fish protein] was maintained in VITAL. There were insufficient data for molluscs, which fall within the definition of "fish" in the ANZ Food Standards Code, and the panel did not make any recommendation in relation to a Reference Dose.

The **Panel recommends a Reference Dose of 1.3 mg finfish protein**, based on the ED_{01} value.

Walnut (and Pecan)

At its current meeting, the Panel considered that there were sufficient data points to establish ED values for walnut (Table 2)[7].

Walnut thresholds were available for 74 individuals (compared to ~15 in 2011). The Panel identified the ED_{01} and ED_{05} for walnut as 0.03mg and 0.8 mg walnut protein respectively (Table 2).

In recognition of the potential for cross-reactivity between walnut and pecan, the **Panel recommends that a new Reference Dose of 0.03 mg be established for walnut and pecan protein**, based on the ED_{01} value for walnut.

Based on the absence of any reports of adverse reactions to tree nuts labelled in accordance with VITAL 2.0, the **Panel recommends that the Reference Dose for tree nuts, other than walnut, pecan, cashew and pistachio, be established at 0.1mg protein**, based on the ED_{01} value for hazelnut.

6. In VITAL 2.0 the Reference Dose for all Tree Nuts, including cashew, was recommended based on hazelnut challenge data

7. In VITAL 2.0 the Reference Dose for all Tree Nuts, including walnut was recommended based on hazelnut challenge data

Table 2 - VSEP recommended Reference Doses (mg protein)

Allergen	No. of individuals	VITAL 2.0 Ref Dose (mg protein)	2019 VSEP Ref Dose (mg protein) [ED_{01}]	Change	2019 VSEP ED_{05} (mg protein)
Egg	431	0.03	**0.2**	↑	2.3
Hazelnut	411	0.1	**0.1**	✓	3.5
Lupin	25	4.0	**2.6**	↓	15.3
Milk	450	0.1	**0.2**	↑	2.4
Mustard	33	0.05	**0.05**	✓	0.4
Peanut	1306	0.2	**0.2**	✓	2.1
Sesame	40	0.2	**0.1**	↓	2.7
Shrimp	75	10.0	**25**	↑	280
Soy (milk + flour)	87	1.0 (soy flour)	**0.5**	↓	10.0
Wheat	99	1.0	**0.7**	↓	6.1
Cashew	245		**0.05**	+	0.8
Celery	82		**0.05**	+	1.3
Fish (finfish)	82		**1.3**	+	12.1
Walnut	74		**0.03**	+	0.8

↑ Reference Dose increased

✓ Reference Dose unchanged

↓ Reference Dose decreased

\+ New Reference Dose

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