

Establishment of Reference Doses for residues of allergenic foods: Report of the VITAL Expert Panel



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ABSTRACT

In 2011, an expert panel was assembled to establish appropriate Reference Doses for allergenic food residues as a part of the VITAL (Voluntary Incidental Trace Allergen Labeling) program of The Allergen Bureau of Australia & New Zealand (ABA). These Reference Doses would guide advisory labeling decisions for use on food labels. Individual NOAELs and LOAELs were obtained from clinical challenges of food-allergic subjects. Statistical dose-distribution models (log-normal, log-logistic, Weibull) were applied to the individual NOAELs and LOAELs for each allergenic food. The Reference Doses, in terms of mg of total protein from the allergenic food, were based upon either the ED₀₁ (for peanut, cow's milk), the 95% lower confidence interval of the ED₀₅ (for wheat, soybean, cashew, shrimp, sesame seed, mustard, and lupine), or both (egg, hazelnut) using all appropriate statistical dose-distribution models. Reference Doses were established for 11 allergenic foods ranging from 0.03 mg for egg protein to 10 mg for shrimp protein. Reference Doses were not established for fish or celery due to poor model fits with existing data. Reference Doses were not established for other tree nuts beyond hazelnut and cashew because of the absence of data on NOAELs and LOAELs from individual subjects.

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1. Introduction

Over the past few decades, food allergies have emerged as a significant public health issue in terms of prevalence and severity. Accordingly, public health authorities and the food industry have placed increasing priority on the protection of food-allergic consumers. Food-allergic individuals must adhere to specific avoidance diets to prevent the occurrence of allergic reactions (Arshad et al., 2007). The labeling of the presence of allergenic foods is critical to the implementation of safe and effective avoidance diets (Sheth et al., 2010). The unintended presence of residues of allergenic foods that are not declared on product labels (undeclared allergens) poses a risk to food-allergic individuals. The implementation of risk assessment approaches is needed to quantify the level of risk and exercise risk management strategies

that would protect food-allergic consumers without being overly burdensome and reducing their quality of life. In particular, it is now well recognized that excessive use of precautionary (advisory) labeling results in unintended consequences, in particular risk-taking which negates the original intent of the labeling (Barnett et al., 2011).

The same principles and approaches of quantitative risk assessment as used for chemical residues in foods also apply to allergenic foods (Spanjersberg et al., 2007, 2010; Madsen et al., 2009). However, in contrast with risk assessment done with chemical residues that rely on toxicological data from experimental animals, useful data exist for food allergens from the actual subset of the human population that have food allergies. Data on individual no-observed adverse effect levels (NOAELs) and lowest-observed adverse effect levels (LOAELs) have emerged from low-dose oral clinical challenge studies with food-allergic individuals that allow the application of quantitative risk assessment approaches and the potential development of population thresholds for specific allergenic foods (Taylor et al., 2010).

Despite the increasing availability of NOAELs and LOAELs determined in food-allergic individuals, public health authorities have

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not established population thresholds for any of the allergenic foods except in Switzerland and Japan where thresholds were established without consideration of NOAELs and LOAELs. In the absence of guidance from public health authorities regarding thresholds, the food industry has implemented the widespread use of various forms of voluntary advisory or precautionary labeling (e.g. may contain x, made on shared equipment with x, etc.) in an attempt to manage the risk and protect food-allergic consumers. As a result, the quality-of-life of food-allergic consumers has decreased (Hourihane et al., 2011). Some food-allergic individuals are even ignoring these advisory statements (Hefle et al., 2007). The proliferation of advisory labeling in Australia (Zurzolo et al., 2013) and the anguish of those food-allergic consumers regarding such labeling prompted the Australian food industry to form The Allergen Bureau of Australia & New Zealand (ABA) (Fleming et al., 2010). In 2007, ABA released their VITAL (Voluntary Incidental Trace Allergen Labeling) program. Its goal was to limit the use of precautionary labeling related to the unintended presence of allergens, for instance through cross-contact, by the use of Action Levels, that were based upon the application of risk assessment principles to the potential doses of exposure, and standardized label messages. Initially, a VITAL grid was established with 3 Action Levels: Green (low risk; no precautionary labeling); Yellow (possible risk; precautionary “may be present: #####” labeling recommended); Red (higher risk; definitive “contains #####” labeling recommended).

The initial VITAL Action Levels were established on the basis of the threshold doses of protein from allergenic foods for subjective and objective responses cited by the 2006 US Food & Drug Administration (FDA) Threshold Working Group (Gendel et al., 2008). Because some uncertainty existed surrounding the FDA estimates and the general paucity of the available data on threshold doses at that time, a 10-fold uncertainty factor was applied. Although it is generally recognized that food-allergic people react to the dose of protein consumed, rather than its concentration, Action Levels in the grid were expressed as concentrations (ppm) which corresponded to an amount of protein (mg) in a 5-g serving size (a teaspoon). Most of the green levels were set at <2 ppm of protein from the allergenic food (exceptions: fish, milk, soy, gluten).

In 2010, the ABA made the decision to revise the VITAL program. Because new data had emerged regarding individual NOAELs and LOAELs for various allergenic foods, together with new methods to analyse them, an expert panel was appointed to evaluate the existing data and make recommendations to ABA regarding the values in the VITAL grid. The following report contains the outcome of expert panel efforts.

2. The process and methods

The VITAL Expert Panel was assembled in the fall of 2010, and a meeting was held in Sydney (Australia) in January 2011. Agreement was reached to use data from oral clinical challenges of individual patients to establish dose distribution relationships for the allergic population using statistical modeling. This approach, which has been described previously (Crevel et al., 2007), introduces the concept of a predicted population eliciting dose (ED), where ED_p refers to the dose of allergen that is predicted to produce a response in p% of the allergic population. The ED is determined from statistically derived population dose distribution curves constructed using the data from clinical challenge studies. The approach enables the identification of a dose of an allergen (ED_p) 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. Agreement was reached to model the dose distributions of as many of the priority allergenic foods as possible (including the Australian, USA, and EU lists of priority allergenic foods).

Initial efforts were made to glean data on individual NOAELs and LOAELs from published clinical literature independently by scientists at the Food Allergy Research & Resource Program (FARRP) at the University of Nebraska and at TNO in the Netherlands. Subsequently, these two sets of data were merged with thorough assessment of any disparities between the data collected by each organization from any published study or individual patient. This curation of the data allowed reassur-

ance that all data points were collected and presented in a uniform manner and avoided accidental double-counting of subjects. Publications were selected based upon the criteria outlined previously (Taylor et al., 2009) in particular focusing on results from low-dose oral challenges. Additionally, unpublished data were obtained where possible and especially from clinical records in the Netherlands and in Berlin, Germany (gathered by TNO) and from partially completed FARRP threshold studies.

Data from DBPCFCs were preferred, except in the case of data from infants and very young children where blinding was not considered absolutely necessary. The available studies involved challenging subjects with increasing doses at intervals until a response was observed. This approach raises the question of whether the reactive dose is the discrete dose given immediately prior to the reaction or the cumulative dose (cumulative of all doses given up to that point). Thus, the data were collected and assessed in terms of both discrete and cumulative data sets. The first objective symptoms of an allergic response occurring in an individual were used as the basis for the LOAEL with the NOAEL set at the previous dose in the clinical protocol; individual LOAELs and NOAELs were recorded in terms of mg of total protein from the specific food. For each subject, the true threshold dose lies, by definition, between the NOAEL and LOAEL doses. Individual threshold data were therefore analyzed using Interval-Censoring Survival Analysis as described previously (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, but who had clear histories of allergic reaction upon consumption of the offending food, were treated as right-censored. Right-censored and especially left-censored data impacted the ED_p estimates but all data were used in reaching decisions about Reference Doses. Other possible clinical data sets where oral challenges were initiated at comparatively high doses (e.g. 500 mg) were excluded from consideration because of the large volume of data points that would be left-censored at those initial comparatively high doses.

The data were fitted to parametric models using the SAS LIFEREG procedure (SAS v9.1) as described previously (Taylor et al., 2009). Three parametric models (log normal, log logistic, Weibull) were used to fit the data for each allergenic food for adults, children (<18 years of age or defined by source as children), and combined adults and children and for discrete doses and cumulative doses.

3. Results

Sufficient low-dose clinical challenge data were obtained to attempt modeling for peanut, milk, egg, hazelnut, soybean, wheat, sesame seed, mustard, lupine, shrimp (for crustacean shellfish), cashew, celery, and fish. No data from low-dose clinical challenges were found for other tree nuts, other crustacean shellfish (crab, lobster), or any molluscan shellfish. Table 1 provides the total number of data points for each of the allergenic foods along with the number of right-censored and left-censored subjects. The number of subjects ranged from a high of 750 subjects for peanut to a low of 19 subjects for fish. The largest data sets existed for peanut, milk, egg and hazelnut with individual thresholds for more than 200 subjects. Most data sets tended to include a higher number of right-censored than left-censored subjects with the exception of milk, egg, fish and celery where a large percentage of the subjects were left-censored. This may skew the dose-distribution curve toward the left potentially resulting in an overly conservative estimate of population threshold. In addition, no data points were obtained for fish and celery for the lower range of the distribution (below the ED₃₀) from the available clinical data. As a result of these two factors, attempts to model these distributions to obtain estimates of eliciting doses were unsuccessful.

The data sets included individual NOAELs and LOAELs from published and unpublished sources (Table 1). The specific source is also provided. Except for cashew (children only) and shrimp (adults only), the data sets included individual thresholds from both children and adults. However, children predominated for some data sets (e.g. milk, egg, and wheat) while adults predominated for others (e.g. hazelnut). The age of the specific patient was not provided for some of the individuals gleaned from publications (age uncertain).

For the purposes of modeling, data from multiple publications and clinics acquired with various clinical challenge protocols were combined. The challenge doses were normalized in all cases to mg of protein from the allergenic food using conversions outlined in

Table 1

Number and sources of threshold data gleaned from publications and unpublished clinical records.

Allergen	Study	Total no. with objective symptoms	Right censored ^a	Left censored ^b	Adults	Children	Age uncertain
<i>Peanut</i>							
Published	Atkins et al. (1985)	2	0	0	2	0	0
	Hourihane et al. (1997)	13	11	0	10	3	0
	Wensing et al. (2002a)	26	20	0	24	2	0
	Lewis et al. (2005)	40	0	3	0	0	40
	Flinterman et al. (2006b)	22	11	0	0	22	0
	Leung et al. (2003)	23	8	1	0	0	23
	Oppenheimer et al. (1992)	4	0	0	1	0	3
	Nelson et al. (1997)	12	0	1	12	0	0
	Taylor et al. (2010) ^c	283	10	7	7	275	1
	Anagnostou et al. (2009)	18	0	7	1	17	0
	Clark et al. (2008, 2009)	5	0	1	0	5	0
	Nicolaou et al. (2010)	10	0	2	0	10	0
	Blumchen et al. (2010)	22	0	2	0	22	0
	Wainstein et al. (2010)	8	0	0	0	8	0
	Patriarca et al. (2006)	1	0	0	1	0	0
Unpublished	Blom et al. (2013)	135	50	5	0	135	0
	WKZ ^d	85	5	1	0	85	0
Total	UMCU ^{e,f}	41	17	0	41	0	0
		750	132	30	99	584	67
<i>Milk</i>							
Published	Staden et al. (2007)	3	0	0	0	3	0
	Norgaard and Bindslev-Jensen (1992)	3	0	1	3	0	0
	Morisset et al. (2003a)	3	0	1	0	0	3
	Caminiti et al. (2009)	11	0	0	0	11	0
	Patriarca et al. (2002)	8	0	0	0	8	0
	Morisset et al. (2007)	11	0	1	0	11	0
	Longo et al. (2008)	60	0	9	0	60	0
	Skripak et al. (2008)	20	0	14	0	20	0
	Lam et al. (2008)	8	2	0	7	1	0
	Hill et al. (1984)	53	0	11	0	53	0
	Fiocchi et al. (2003)	12	0	5	0	12	0
	Baehler et al. (1996)	10	0	0	0	10	0
	Flinterman et al. (2006a)	11	0	3	0	11	0
	Orhan et al. (2009)	4	0	0	0	4	0
	Devenney et al. (2006)	2	0	1	0	2	0
	Høst and Samuelsson (1988)	3	0	2	0	3	0
	Blom et al. (2013)	93	13	7	0	93	0
Unpublished	UMCU ^e	15	4	1	15	0	0
	JBZ ^g	21	0	3	0	21	0
Total		351	19	59	25	323	3
<i>Egg</i>							
Published	Staden et al. (2007)	3	0	1	0	3	0
	Benhamou et al. (2008)	33	0	9	0	33	0
	Morisset et al. (2003a)	20	0	4	0	0	20
	Caffarelli et al. (1995)	13	0	0	0	13	0
	Morisset et al. (2007)	15	0	0	0	15	0
	Atkins et al. (1985)	1	0	0	1	0	0
	Norgaard and Bindslev-Jensen (1992)	7	0	0	6	1	0
	Knight et al. (2006)	7	0	5	0	7	0
	Unsel et al. (2007)	1	0	0	1	0	0
	Orhan et al. (2009)	3	0	0	0	3	0
	Eggesbø et al. (2001)	7	0	1	0	7	0
	Blom et al. (2013)	53	13	2	0	53	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
<i>Hazelnut</i>							
Published	Wensing et al. (2002b)	29	27	1	29	0	0
	Blom et al. (2013)	28	11	2	0	28	0
Unpublished	UMCU ^e	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
<i>Soybean</i>							
Published	Ballmer-Weber et al. (2007)	22	11	0	0	0	22
	Zeiger et al. (1999)	9	0	0	0	9	0

(continued on next page)

Table 1 (continued)

Allergen	Study	Total no. with objective symptoms	Right censored ^a	Left censored ^b	Adults	Children	Age uncertain
Unpublished	Magnolfi et al. (1996)	5	1	2	0	5	0
	Fiocchi et al. (2003)	7	0	1	0	7	0
	FARRP ^h	8	3	0	6	2	0
	UBer ⁱ	17	4	2	17	0	0
	UMCG ^j	10	7	1	0	10	0
	UMCU ^e	2	2	0	2	0	0
Total		80	28	6	25	33	22
<i>Wheat</i>							
Published	Ito et al. (2008)	21	0	1	0	21	0
	Pastorello et al. (2007)	3	1	1	0	3	0
	Scibilia et al. (2006)	13	0	3	12	1	0
Unpublished	UMCG ^j	3	0	0	0	3	0
Total		40	1	5	12	28	0
<i>Cashew</i>							
Published	Blom et al. (2013)	31	16	1	0	31	0
Total		31	16	1	0	31	0
<i>Mustard</i>							
Published	Figueroa et al. (2005)	14	10	0	9	5	0
	Morisset et al. (2003b)	4	0	0	0	4	0
	Rancé et al. (2000)	15	0	2	0	15	0
Total		33	10	2	9	24	0
<i>Lupine</i>							
Published	Moneret-Vautrin et al. (1999)	5	0	0	0	5	0
	Fiocchi et al. (2009)	2	0	1	0	2	0
	Shaw et al. (2008)	2	0	0	0	2	0
Unpublished	UMCU ^e	15	7	1	15	0	0
Total		24	7	2	15	9	0
<i>Sesame seed</i>							
Published	Leduc et al. (2006)	12	0	1	7	5	0
	Morisset et al. (2003a)	1	0	0	0	0	1
	Kolopp-Sarda et al. (1998)	1	0	0	0	0	1
	Kanny et al. (1996)	7	1	1	6	1	0
Total		21	1	2	13	6	2
<i>Shrimp</i>							
Published	Atkins et al. (1985)	4	0	0	4	0	0
	Daul et al. (1988)	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 Kinderziekenhuis Children's Hospital of the University Medical Center Utrecht, The Netherlands.

^e UMCU – University Medical Center Utrecht, The Netherlands.

^f Include Peeters et al. (2007).

^g JBZ – Joroen Bosch Hospital, The Netherlands.

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

ⁱ Universitätsmedizin Berlin, Germany.

^j UMCU – University Medical Center Groningen, The Netherlands.

Table 2. While the form of the food and the degree of processing of that food varied between clinics, these differences were ignored for the purposes of this analysis due to insufficient data for statistical comparisons.

The three parametric models were applied to yield estimates of the ED₀₁ (for peanut, milk, egg, and hazelnut where >200 data points existed) and the 95% lower confidence interval of the ED₀₅ for foods where fewer data points were available (soybean, wheat, sesame seed, lupine, mustard, cashew, and shrimp). Both ED estimates were done for egg and hazelnut where the number of data points was considered borderline for estimation of the ED₀₁. Table 3 provides these ED estimates for each of the appropriate parametric models for adults, children, and combined adult plus children (including all subjects of uncertain age); for some foods, insufficient data were available for adults to allow modeling. In each case, the panel examined each of the dose-distribution

models visually to determine if any of the models failed to match the actual data points especially for the lower doses in the distribution. In several cases (peanut and milk), the Weibull model did not fit well with the actual data so the ED estimates for this model were excluded. Fig. 1 displays the dose-distribution for peanut for all three parametric models demonstrating how the actual data diverge from the Weibull model at the lowest doses. The Weibull model yielded the most conservative ED estimates in all cases. Table 3 also provides ED estimates for both discrete and cumulative doses. While use of the discrete dose is, in most cases, the most conservative choice for risk assessment purposes, little difference existed between the ED values based on discrete vs. cumulative doses for any of the parametric models.

The Panel considered the ED values from all of the appropriate parametric models to identify a recommended Reference Dose for each of the allergenic foods (Table 3). In some cases (e.g. egg), the

Table 2

Conversion factors used to normalize the threshold challenge material.

Food	Conversion to	Protein content (%)	mg Protein	mg Food	Reference
Peanut	Whole peanut	25.0	1	4.0	Taylor et al. (2002)
Peanut	Defatted peanut flour	50.0	1	2.0	Taylor et al. (2002)
Milk	Liquid milk	3.3	1	30.3	USDA ^a – 2% milk
Milk	NFDM	35.1	1	2.8	USDA ^a – instant NFDM
Egg	Raw whole egg	12.6	1	8.0	USDA ^a
Egg	Raw egg white	10.5	1	9.5	NEVO ^b
Egg	Cooked whole egg	12.6	1	7.9	USDA ^a
Egg	Cooked egg white	10.5	1	9.5	NEVO ^b
Egg	Dried whole egg	46.0	1	2.2	NEVO ^b
Egg	Dried egg white	81.1	1	1.2	USDA ^a
Hazelnut	Hazelnut flour	15.7	1	6.4	Wensing et al. (2002b)
Soy	Whole soybean	40.0	1	2.5	VITAL Expert Panel
Soy	Soy flour	53.0	1	1.9	Ballmer-Weber et al. (2007)
Soy	Soy milk	3.6	1	27.8	Provided by UMCU ^c
Wheat	Raw or cooked wheat flour	10.0	1	10.0	NEVO ^b and USDA ^a
Cashew	Cashew flour	19.0	1	5.3	NEVO ^a
Mustard	Mustard seed	26.1	1	3.8	USDA ^a – S. alba seed
Lupin	Lupin flour	36.2	1	2.8	USDA ^a
Lupin	Yellow lupin flour	40.0	1	2.5	Shaw et al. (2008)
Sesame	Crushed sesame seeds	17.0	1	5.9	USDA ^a – roasted seed
Sesame	Sesame seed flour	30.8	1	3.2	USDA ^a – high fat flour
Shrimp	Whole cooked shrimp	22.8	1	4.4	USDA ^a – steamed/boiled

The protein levels listed in Table 2 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.

^a USDA, US Department of Agricultural National Nutrient Database.

^b Dutch Food Composition Table.

^c UMCU – University Medical Center Utrecht.

most conservative model was used as the basis for the Reference Dose when the actual data seemed to fit that model quite well. In cases such as peanut where two or more models seemed to fit the data equally well, the Reference Dose was selected from an average of the projections. The allergenic foods with the lowest eliciting doses on a protein basis were egg and mustard with Reference Doses of 0.03 mg of egg protein and 0.05 mg of mustard protein respectively. Somewhat surprisingly, the Reference Dose for peanut (0.2 mg peanut protein) was higher than that for egg, mustard, milk, and hazelnut. The allergenic food with the highest eliciting dose on a protein basis is shrimp with a Reference Dose of 10 mg of shrimp protein equivalent to 44 mg of shrimp (see Table 3).

4. Discussion

Sufficient data were available from low-dose oral clinical challenges to allow estimation of the ED₀₁ and/or the 95% lower confidence interval of the ED₀₅ for 11 commonly allergenic foods. The selection of the ED₀₁ as the basis for the VITAL Reference Doses protects 99% of the population allergic to the particular food from any objective reaction. The use of the ED₀₁ dose also likely minimizes the probability of anything more serious than a mild reaction occurring in the remaining 1%. However, the possibility of a more severe reaction occurring in a small fraction of this remaining 1% of the allergic population cannot be excluded. Ideally, this remaining 1% of the allergic population would be clinically identified and receive additional clinical advice to manage their condition in the manner similar to the small percentage of milk-allergic individuals who are reactive to hypoallergenic infant formula (Rosenthal et al., 1991; Saylor and Bahna, 1991). Traditionally, the term, hypoallergenic, has been applied to infant formula on the basis of clinical trials of milk-allergic infants that provide 95% assurance that 90% of milk-allergic infants will not react to the formula, the 95% lower confidence interval of the ED₁₀. The Expert Panel judged that the choice of the 99% level of

protection afforded an optimal public health outcome, striking a balance between level of protection, ability to verify analytically and therefore enforcement, and consumer observance of precautionary labeling. Furthermore, the available data, even for foods for which they were most abundant, do not allow to derive, with a good degree of statistical confidence, ED values below the ED₀₁. In situations where the data were insufficient to allow robust estimation of the ED₀₁ (<200 data points), the lower 95% confidence interval of the ED₀₅ was utilized. This eliciting dose would likely protect 97–98% of the affected population. With smaller data sets where estimation of the ED₀₁ was not robust and the confidence intervals surrounding the ED₀₅ were wider, the selection of the lower 95% confidence interval as the basis for the Reference Dose provided more conservatism and provided a greater degree of consumer protection. The lower 95% confidence interval was not applied to the ED₀₁ estimates for peanut, hazelnut, milk, and egg because the 99% level of protection was deemed adequate by the Expert Panel.

The Panel decided that there was no need to apply additional uncertainty factors to develop the VITAL Reference Doses because low ED estimates were used, data were available from the appropriate sub-population of humans, and the adverse reactions experienced by patients in these low-dose oral clinical challenges were mild to moderate. Other clinical investigators have noted that some patients in diagnostic oral challenge trials experience severe reactions even on administration of the first dose (Perry et al., 2004). However, in these cases, the oral challenges were initiated at comparatively high dose levels, typically 500 mg and always ≥100 mg. In contrast, the clinical data used here came from oral challenges initiated at much lower doses (variable among clinics) that never resulted in provocation of severe reactions; severe reactions were defined as outlined in Taylor et al. (2010). The Expert Panel acknowledged that circumstances would occur (infections, sub-optimal use of medication, strenuous exercise) where certain patients might have a lower minimum eliciting dose. In such situations, patients might be advised to exercise more care in their avoidance diets (e.g. avoiding certain categories of packaged food

Table 3

Reference Doses for 11 allergenic foods based parametric modeling of minimal eliciting doses from food-allergic populations.

Allergen	Distribution model		ED01 (mg protein)		95% Lower confidence interval of ED05 (mg protein)		Reference Dose (mg protein)
			Discrete dosing	Cumulative dosing	Discrete dosing	Cumulative dosing	
Peanut	LogLogistic	Children	0.14	0.18			0.2 mg
		Adults	0.21	0.26			
		Pooled	0.1	0.13			
	LogNormal	Children	0.27	0.34			
		Adults	0.57	0.72			
		Pooled	0.22	0.28			
Milk	LogLogistic	Children	0.083	0.14			0.1 mg
		Adults	4.2	4.7			
		Pooled	0.081	0.14			
	LogNormal	Children	0.22	0.35			
		Adults	5.4	5.9			
		Pooled	0.21	0.34			
Egg	LogLogistic	Children	0.13	0.12	0.69	0.66	0.03 mg
	LogNormal	Children	0.21	0.2	0.62	0.62	
	Weibull	Children	0.045	0.03	0.38	0.31	
Hazelnut	LogLogistic	Children	0.15	0.17	0.49	0.55	0.1 mg
		Adults	0.087	0.23	0.51	1.2	
		Pooled	0.11	0.21	0.69	1.3	
	LogNormal	Children	0.15	0.16	0.32	0.35	
		Adults	0.32	0.69	0.92	1.9	
		Pooled	0.25	0.42	0.84	1.4	
	Weibull	Children	0.047	0.053	0.99	0.26	
		Adults	0.011	0.033	0.48	0.36	
		Pooled	0.017	0.038	0.23	0.46	
	LogLogistic	Pooled			1.0	2.9	
Soy flour/infant formula	LogNormal	Pooled			2.3	5.5	1.0 mg
	Weibull	Pooled			0.15	0.5	
Wheat	LogLogistic	Pooled			1.5	1.3	1.0 mg
	LogNormal	Pooled			1.6	1.4	
	Weibull	Pooled			0.44	0.41	
Cashew	LogLogistic	Children			3	3.3	Provisional 2.0 mg
	LogNormal	Children			2.6	3	
	Weibull	Children			1.9	2.1	
Mustard	LogLogistic	Pooled			0.09	0.1	0.05 mg
	LogNormal	Pooled			0.11	0.12	
	Weibull	Pooled			0.046	0.052	
Lupin	LogLogistic	Pooled			4.8	4.5	4.0 mg
	LogNormal	Pooled			6.5	6.1	
Sesame seed	LogLogistic	Pooled			0.45	0.56	0.2 mg
	LogNormal	Pooled			0.49	0.61	
	Weibull	Pooled			0.13	0.18	
Shrimp	LogLogistic	Adults			17.6	19.1	10 mg
	LogNormal	Adults			10.4	12.1	
	Weibull	Adults			13.1	13.9	

where cross contact is more likely such as bakery items and chocolate confections).

The Expert Panel applied three different dose-distribution models (log normal, log logistic, Weibull) to the challenge data for each food. No biological rationale exists to select one model over another. Accordingly, the Expert Panel evaluated the ED values from all of the appropriate models (Table 3) to discern the Reference Dose for each allergenic food. The Weibull model was not used for peanut and milk because the actual data did not fit that model at the lower end of the dose distribution as illustrated for peanut (Fig. 1). The Weibull model was the most conservative model estimating the lowest ED values. In some cases (e.g. egg), the Weibull model influenced the selection of a low Reference Dose. However, in the case of lupine, the Weibull model was not used because of the absence of data at the lower doses documenting that this conservatism of the model was realistic.

Sufficient data were only available for peanut to allow effective comparison of ED estimates for children and adults. In the case of peanut, data were available from 584 children and 99 adults (and an additional 67 individuals of uncertain age). For peanut, the ED estimates do suggest that the population of peanut-allergic children is more sensitive than peanut-allergic adults but the difference was small. In most cases including peanut, the pooled ED estimates were also made to allow the most robust statistical estimate. For milk, data were available for only 25 adults compared to 323 children so the Reference Dose was developed based upon the ED estimates for the pooled and children data. For egg, data were available for only 12 adults so the Reference Dose was developed only using the ED estimates for children where data from 174 children were available. For soybean, most of the data were derived from children or individuals of uncertain age so only the pooled data were used for the ED estimates. For wheat, limited

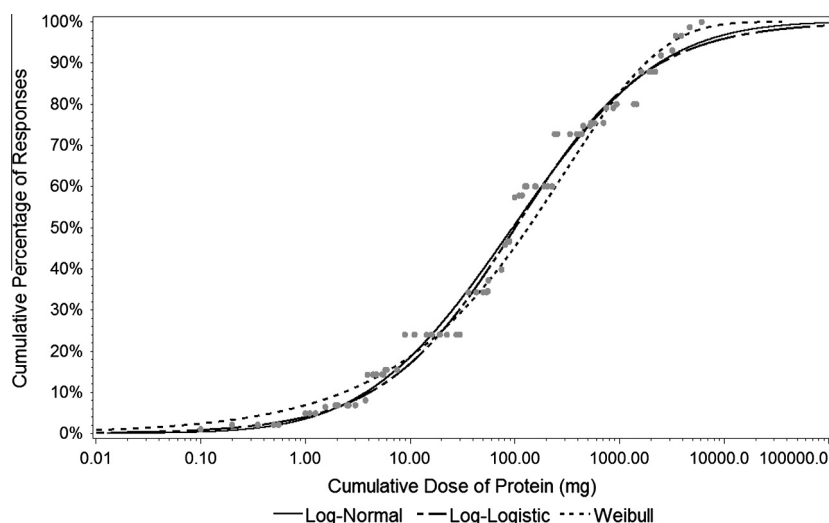


Fig. 1. Probability distribution models for individual peanut thresholds (expressed as mg protein).

data were available from adults so the ED estimates were based primarily from the pooled data and the data for children. For mustard, sesame seed, and lupine, a limited amount of data was available so the ED estimates were based on pooled data to allow the most robust statistical comparison among the models. With cashew, all of the available data were obtained from children. Since cashew allergy exists in adults, acquisition of data from adults would be helpful and the recommended Reference Dose is considered as provisional based upon that data gap. For shrimp, all of the available data were from adults but shrimp allergy occurs primarily in adults and older children. For the analysis with most of the 11 foods, challenge data were pooled from multiple clinics in several countries. A more in-depth analysis of these data has indicated that geographic differences do not occur and confirmed that age differences do not occur for those foods where sufficient information exists to do a comparison, namely peanut and hazelnut (Allen et al., *in press*). However, patient selection bias and the choice of the dosage scheme for challenges can influence ED_p estimates (Allen et al., *in press*).

While various forms of food were used in the oral clinical challenges, these differences were ignored since insufficient data existed to make comparisons except in the case of soybeans. With soybeans, data were available from 51 challenges conducted either with soy flour or soy-based infant formula. The Reference Dose for soy was based on these data. Recently however, some soy-allergic patients have been described who react to certain brands of soy milk but can safely ingest soy flour and other forms of soy (Mittag et al., 2004). These patients, primarily adults and older children, have very low minimum eliciting doses for soybean in the form of soy milk. These individuals appear to be a subset of the soy-allergic population that merits further investigation. This observation illustrates that processing may have some effect on minimum eliciting doses for individuals with specific food allergies. Processing effects are best documented for egg and milk (Nowak-Węgrzyn and Fiocchi, 2009). For example, recent clinical studies have documented that some egg-allergic children are more tolerant of baked egg than of raw egg (Des Roches et al., 2006; Eigenmann, 2000; Osborne et al., 2011). In the investigations evaluated here, both raw and cooked eggs were used as challenge materials. These two materials are likely not equivalent but the Panel decided to consider them as equivalent in this assessment, while acknowledging the drawbacks of doing so. The effects of processing with respect to egg represent another data gap that should be assessed in the future. The Panel would observe that clinical studies are often done

with raw egg but that consumers rarely eat raw egg and perhaps should not due to other food safety concerns.

The Reference Doses recommended in Table 3 relate specifically to IgE-mediated food allergies and not to other forms of food allergy/sensitivity that might be associated with any of these foods. However, with wheat, the Codex Alimentarius Commission has established a guideline for gluten-free of <20 ppm for specialty foods intended for individuals with celiac disease, which has also been adopted by various legislatures, such as the EU. However, with a Reference Dose of 1 mg of wheat protein, individuals with IgE-mediated wheat allergy would be largely protected when selecting gluten-free products manufactured in conformity to Codex guidance.

The VITAL Reference Doses are intended to guide the application of precautionary labels onto food products. Thus, if the ingestion of a particular food is likely to allow the dose of an allergenic food to exceed its Reference Dose, then precautionary labeling is recommended. However, the dose of the allergenic food depends on the concentration of the allergenic food residues in the product and the amount of the particular food that is consumed. Quantitative risk assessment can be conducted by the combined consideration of the dose-distribution of individual thresholds (Fig. 1), the distribution of concentrations of allergenic food residues found in the product in question, and the range of consumption levels for the particular product or product category within the population (Spanjersberg et al., 2007, 2010; Kruizinga et al., 2008; Rimbaud et al., 2010; Robertson et al., 2013; Remington et al., 2013). Foods typically consumed in small amounts (e.g. condiments) would result in lower doses of the allergenic food by comparison to foods (e.g. main course) consumed in much larger amounts. Consumption ranges for specific products should be considered when reaching decisions about the need to apply precautionary allergen labels and the allergen concentrations (action levels) that would trigger such labeling.

The food industry commonly uses shared equipment and facilities to manufacture multiple packaged food products. As consumer awareness about food allergies grew over the past 10–15 years, consumers increasingly began to inquire about such shared use of equipment and facilities. In response to these inquiries, the food industry voluntarily began to apply precautionary allergen labeling statement (e.g. may contain x) to food products. In the absence of guidance regarding appropriate Reference Doses, the use of precautionary allergen labeling proliferated greatly in many countries including Australia (Fleming et al., 2010). The

VITAL program was initiated in 2007 as a voluntary approach by the food industry to establish appropriate parameters (Reference Doses) to ensure that precautionary labeling was used only when appropriate and relevant to some genuine level of risk posed to allergic consumers (Fleming et al., 2010). Currently allergic consumers are frustrated by the perceived over-use of precautionary labeling (Turner et al., 2011). The success of any program such as VITAL is predicated upon selection of Reference Doses that protect the vast majority of the food-allergic population while allowing access to the widest possible variety of packaged foods. The proliferation of precautionary labeling is acknowledged to detract from the quality of life of food-allergic individuals (Hourihane et al., 2011). Also because of the widespread use of precautionary allergen labeling, evidence exists that some food-allergic consumers ignore precautionary label statements (Hefle et al., 2007). Ideally, the use of the VITAL program with appropriate Reference Doses would increase the value of the label, restrict the use of precautionary labeling statements in a manner related to some level of risk, and enhance the quality of life of food-allergic consumers.

Conflict of Interest

The authors declare that there are no conflicts of interest.

References

- Allen, K.J., Remington, B.C., Baumert, J.L., Crevel, R.W.R., Houben, G.F., Brooke-Taylor, S., Kruijzinga, A.G., Taylor, S.L., 2013. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J. Allergy Clin. Immunol.* <http://dx.doi.org/10.1016/j.jaci.2013.06.042>.
- Anagnostou, K., Islam, S., King, Y., Deighton, J., Clark, A.T., Ewan, P.W., 2009. Induction of tolerance in severe peanut allergy. *Clin. Exp. Allergy* 39, 1954.
- Arshad, S.H., Bateman, B., Sadeghnejad, A., Gant, C., Matthews, S.M., 2007. Prevention of allergic disease during childhood by allergen avoidance: the Isle of Wight prevention study. *J. Allergy Clin. Immunol.* 119, 307–313.
- Atkins, F.M., Steinberg, S.S., Metcalfe, D.D., 1985. Evaluation of immediate adverse reactions to foods in adult patients II. A detailed analysis of reaction patterns during oral food challenge. *J. Allergy Clin. Immunol.* 75, 356–363.
- Baehler, P., Chad, Z., Gurbindo, C., Bonin, A.P., Bouthillier, L., Seidman, E.G., 1996. Distinct patterns of cow's milk allergy in infancy defined by prolonged, two-stage double-blind, placebo-controlled food challenges. *Clin. Exp. Allergy* 26, 254–261.
- Ballmer-Weber, B.K., Holzhauser, T., Scibilia, J., Mittag, D., Zisa, G., Ortolani, C., Oesterballe, M., Poulsen, L.K., Vieths, S., Bindslev-Jensen, C., 2007. Clinical characteristics of soybean allergy in Europe: a double-blind, placebo-controlled food challenge study. *J. Allergy Clin. Immunol.* 119, 1489–1496.
- Barnett, J., Leftwich, J., Muncer, K., Grimshaw, K., Shepherd, R., Raats, M.M., Gowland, M.H., Lucas, J.S., 2011. How do peanut and nut-allergic consumers use information on the packaging to avoid allergens? *Allergy* 66, 969–978.
- Benhamou, A.H., Zamora, S.A., Eigenmann, P.A., 2008. Correlation between specific immunoglobulin E levels and the severity of reactions in egg allergic patients. *Ped. Allergy Immunol.* 19, 173–179.
- Blom, W.M., Vlieg-Boerstra, B.J., Kruijzinga, A.G., van der Heide, S., Houben, G.F., Dubois, A.E.J., 2013. Threshold dose distributions for 5 major allergenic foods in children. *J. Allergy Clin. Immunol.* 131, 172–179.
- Blumchen, K., Ulbricht, H., Staden, U., Dobberstein, K., Beschoner, J., de Oliveira, L.C.L., Shreffler, W.G., Sampson, H.A., Niggemann, B., Wahn, U., Beyer, K., 2010. Oral peanut immunotherapy in children with peanut anaphylaxis. *J. Allergy Clin. Immunol.* 126, 83–91.
- Caffarelli, C., Cavagni, G., Giordano, S., Stapane, I., Rossi, C., 1995. Relationship between oral challenges with previously uningested egg and egg-specific IgE antibodies and skin prick tests in infants with food allergy. *J. Allergy Clin. Immunol.* 95, 1215–1220.
- Caminiti, L., Passalacqua, G., Barberi, S., Vita, D., Barberio, G., De Luca, R., Pajno, G.B., 2009. A new protocol for specific oral tolerance induction in children with IgE-mediated cow's milk allergy. *Allergy Asthma Proc.* 30, 443–448.
- Clark, A.T., King, Y., Islam, S., Anagnostou, K., Deighton, J., Ewan, P.W., 2008. The study of tolerance to oral peanut (STOP). *Clin. Exp. Allergy* 38, 1995.
- Clark, A.T., Islam, S., King, Y., Deighton, J., Anagnostou, K., Ewan, P.W., 2009. Successful oral tolerance induction in severe peanut allergy. *Allergy* 64, 1218–1220.
- Crevel, R.W.R., Briggs, D., Hefle, S.L., Knulst, A.C., Taylor, S.L., 2007. Hazard characterisation in food allergen risk assessment: the application of statistical approaches and the use of clinical data. *Food Chem. Toxicol.* 45, 691–701.
- Daul, C.B., Morgan, J.E., Hughes, J., Lehrer, S.B., 1988. Provocation-challenge studies in shrimp-sensitive individuals. *J. Allergy Clin. Immunol.* 81, 1180–1186.
- Des Roches, A., Nguyen, M., Paradis, L., Primeau, M.N., Singer, S., 2006. Tolerance to cooked egg in an egg allergic population. *Allergy* 61, 900–901.
- Devenney, I., Norrman, G., Oldæus, G., Strömberg, L., Fälth-Magnusson, K., 2006. A new model for low-dose food challenge in children with allergy to milk or egg. *Acta Paediatrica* 95, 1133–1139.
- Eggesbø, M., Botten, G., Halvorsen, R., Magnus, P., 2001. The prevalence of allergy to egg: a population-based study in young children. *Allergy* 56, 403–411.
- Eigenmann, P.A., 2000. Anaphylactic reactions to raw eggs after negative challenges with cooked eggs. *J. Allergy Clin. Immunol.* 105, 587–589.
- Figuerola, J., Blanco, C., Dumpierrez, A.G., Almeida, L., Ortega, N., Castillo, R., Navarro, L., Perez, E., Gallego, M.D., Carrillo, T., 2005. Mustard allergy confirmed by double-blind placebo-controlled food challenges: clinical features and cross-reactivity with mugwort pollen and plant-derived foods. *Allergy* 60, 48–55.
- Fiocchi, A., Travaini, M., D'Auria, E., Banderali, G., Bernardo, L., Riva, E., 2003. Tolerance to a rice hydrolysate formula in children allergic to cow's milk and soy. *Clin. Exp. Allergy* 33, 1576–1580.
- Fiocchi, A., Sarratut, P., Terracciano, L., Vacca, E., Bernardini, R., Fuggetta, D., Ballabio, C., Duranti, M., Magni, C., Restani, P., 2009. Assessment of the tolerance to lupine-enriched pasta in peanut-allergic children. *Clin. Exp. Allergy* 39, 1045–1051.
- Fleming, F., Grinter, K., Leighton, K., Norman, K., Preston, C., Said, M., 2010. The challenges of precautionary labeling. In: Boye, J.L., Godefroy, S.B. (Eds.), *Allergen Management in the Food Industry*. John Wiley & Sons Inc., Hoboken, NJ, pp. 453–472.
- Flinterman, A.E., Knulst, A.C., Meijer, Y., Bruijnzeel-Koomen, C.A.F.M., Pasmans, S.G.M.A., 2006a. Acute allergic reactions in children with AEDS after prolonged cow's milk elimination diets. *Allergy* 61, 370–374.
- Flinterman, A.E., Pasmans, S.G., Hoekstra, M.O., Meijer, Y., van Hoffen, E., Knol, E.F., Hefle, S.L., Bruijnzeel-Koomen, C.A., Knulst, A.C., 2006b. Determination of no-observed-adverse-effect levels and eliciting doses in a representative group of peanut-sensitized children. *J. Allergy Clin. Immunol.* 117, 448–454.
- Gendel, S., Buchanan, R., Dennis, S., Acheson, D., Assimon, S.A., Beru, N., Bolger, P., Carlson, D., Carvajal, R., Copp, C., Falci, K., Garber, E., Harden, E., Kane, R., Kvenberg, J., Luccioli, S., Park, D., Raybourne, R., Troxell, T., Vierk, K. Threshold Working Group, 2008. Approaches to establish thresholds for major food allergens and for gluten in food. *J. Food Prot.* 71, 1043–1088.
- Hefle, S.L., Furlong, T.J., Niemann, L., Lemon-Mule, H., Sicherer, S., Taylor, S.L., 2007. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J. Allergy Clin. Immunol.* 120, 171–176.
- Hill, D.J., Ford, R.P.K., Shelton, M.J., Hosking, C.S., 1984. A study of 100 infants and young children with cow's milk allergy. *Clin. Reviews Allergy* 2, 125–142.
- Høst, A., Samuelsson, E.-G., 1988. Allergic reactions to raw, pasteurized, and homogenized/pasteurized cow milk: a comparison. *Allergy* 43, 113–118.
- Hourihane, J.O.'B., Kilburn, S.A., Nordlee, J.A., Hefle, S.L., Taylor, S.L., Warner, J.O., 1997. An evaluation of the sensitivity of subjects with peanut allergy to very low doses of peanut protein: a randomized, double-blind, placebo-controlled food challenge study. *J. Allergy Clin. Immunol.* 100, 596–600.
- Hourihane, J.O.B., Dubois, A.E.J., Flokstra-de Blok, B., Dunn-Galvin, A., 2011. Impact of food challenge tests on children's and parent's health related quality of life: a time series case-control study. *J. Allergy Clin. Immunol.* 127, AB 242.
- Ito, K., Futamura, M., Borres, M.P., Takaoka, Y., Dahlström, J., Sakamoto, T., Tanaka, A., Kohno, K., Matsuo, H., Morita, E., 2008. IgE antibodies to ω -5 gliadin associate with immediate symptoms on oral wheat challenge in Japanese children. *Allergy* 63, 1536–1542.
- Kanny, G., De Hauteclouque, C., Moneret-Vautrin, D.A., 1996. Sesame seed and sesame seed oil contain masked allergens of growing importance. *Allergy* 51, 952–957.
- Knight, A.K., Shreffler, W.G., Sampson, H.A., Sicherer, S.H., Noone, S., Mofidi, S., Nowak-Węgrzyn, A., 2006. Skin prick test to egg white provides additional diagnostic utility to serum egg white-specific IgE antibody concentration in children. *J. Allergy Clin. Immunol.* 117, 842–847.
- Kolopp-Sarda, M.N., Moneret-Vautrin, D.A., Gobert, B., Kanny, G., Brodschii, M., Bene, M.C., Faure, G.C., 1998. Specific humoral immune responses in 12 cases of food sensitization to sesame seed. *Clin. Exp. Allergy* 27, 1285–1291.
- Kruijzinga, A.G., Briggs, D., Crevel, R.W.R., Knulst, A.C., van den Bosch, L.M.C., Houben, G.F., 2008. Probabilistic risk assessment model for allergens in foods: sensitivity analysis for the minimum eliciting dose and food consumption. *Food Chem. Toxicol.* 46, 1437–1443.
- Lam, H.Y., van Hoffen, E., Michelsen, A., Guikers, K., van der Tas, C.H.W., Bruijnzeel-Koomen, C.A.F.M., Knulst, A.C., 2008. Cow's milk allergy in adults is rare but severe: both casein and whey proteins are involved. *Clin. Exp. Allergy* 38, 995–1002.
- Leduc, V., Moneret-Vautrin, D.A., Tzen, J.T.C., Morisset, M., Guerin, L., Kanny, G., 2006. Identification of oleosins as major allergens in sesame seed allergic patients. *Allergy* 61, 349–356.
- Leung, D.Y.M., Sampson, H.A., Yunginger, J.W., Burks Jr., A.W., Schneider, L.C., Wortel, C.H., Davis, F.M., Hyun, J.D., Shanahan, W.R., 2003. Effect of anti-IgE therapy in patients with peanut allergy. *N. Eng. J. Med.* 348, 986–993.
- Lewis, S.A., Grimshaw, K.E.C., Warner, J.O., Hourihane, J.O.B., 2005. The promiscuity of immunoglobulin E binding to peanut allergens, as determined by Western blotting, correlates with the severity of clinical symptoms. *Clin. Exp. Allergy* 35, 767–773.
- Longo, G., Barbi, E., Berti, I., Meneghetti, R., Pittalis, A., Ronfani, L., Ventura, A., 2008. Specific oral tolerance induction in children with very severe cow's milk-induced reactions. *J. Allergy Clin. Immunol.* 121, 343–347.
- Madsen, C.B., Hattersley, S., Buck, J., Gendel, S.M., Houben, G.F., Hourihane, J.O.B., Mackie, A., Mills, E.N.C., Norhede, P., Taylor, S.L., Crevel, R.W.R., 2009.

- Approaches to risk assessment in food allergy: report from a workshop developing a framework for assessing the risk from allergenic foods. *Food Chem Toxicol.* 47, 480–489.
- Magnolfi, C.F., Zani, G., Lacava, L., Patria, M.F., Bardare, M., 1996. Soy allergy in atopic children. *Annals Allergy Asthma Immunol.* 77, 197–201.
- Mittag, D., Vieths, S., Vogel, L., Becker, W.-M., Rihs, H.-P., Helbling, A., Wüthrich, B., Ballmer-Weber, B.K., 2004. Soybean allergy in patients allergic to birch pollen: clinical investigation and molecular characterization of allergens. *J. Allergy Clin. Immunol.* 113, 148–154.
- Moneret-Vautrin, D.A., Guérin, L., Kanny, G., Flabbee, J., Frémont, S., Morisset, M., 1999. Cross-allergenicity of peanut and lupine: the risk of lupine allergy in patients allergic to peanuts. *J. Allergy Clin. Immunol.* 104, 883–888.
- Morisset, M., Moneret-Vautrin, D.A., Kanny, G., Guénard, L., Beaudouin, E., Flabbee, J., Hatahet, R., 2003a. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. *Clin. Exp. Allergy* 33, 1046–1051.
- Morisset, M., Moneret-Vautrin, D.A., Maadi, F., Frémont, S., Guénard, L., Croizier, A., Kanny, G., 2003b. Prospective study of mustard allergy: first study with double-blind placebo-controlled food challenge trials (24 cases). *Allergy* 58, 295–299.
- Morisset, M., Moneret-Vautrin, D.A., Guénard, L., Cuny, J.M., Frentz, P., Hatahet, R., Hanss, C.H., Beaudouin, E., Petit, N., Kanny, G., 2007. Oral desensitization in children with milk and egg allergies obtains recovery in a significant proportion of cases. A randomized study in 60 children with cow's milk allergy and 90 children with egg allergy. *Eur. Annals Allergy Clin. Immunol.* 39, 12–19.
- Nelson, H.S., Lahr, J., Rule, R., Bock, A., Leung, D., 1997. Treatment of anaphylactic sensitivity to peanuts by immunotherapy with injections of aqueous peanut extract. *J. Allergy Clin. Immunol.* 99, 744–751.
- Nicolaou, N., Poorafshar, M., Murray, C., Simpson, A., Winell, H., Kerry, G., Harlin, A., Woodcock, A., Ahlstedt, S., Custovic, A., 2010. Allergy or tolerance in children sensitized to peanut: prevalence and differentiation using component-resolved diagnostics. *J. Allergy Clin. Immunol.* 125, 191–197.
- Norgaard, A., Bindslev-Jensen, C., 1992. Egg and milk allergy in adults: diagnosis and characterization. *Allergy* 47, 503–509.
- Nowak-Węgrzyn, A., Fiocchi, A., 2009. Rare, medium, or well done? The effect of heating and food matrix on food protein allergenicity. *Curr. Opin. Allergy Clin. Immunol.* 9, 234–237.
- Oppenheimer, J.J., Nelson, H.S., Bock, S.A., Christensen, F., Leung, D.Y.M., 1992. Treatment of peanut allergy with rush immunotherapy. *J. Allergy Clin. Immunol.* 90, 256–262.
- Orhan, F., Karakas, T., Cakir, M., Aksoy, A., Baki, A., Gedik, Y., 2009. Prevalence of immunoglobulin E-mediated food allergy in 6–9-year-old urban schoolchildren in the eastern Black Sea region of Turkey. *Clin. Exp. Allergy* 39, 1027–1035.
- Osborne, N., Koplin, J.J., Martin, P.E., Gurrin, L.C., Lowe, A.J., Matheson, M.C., Ponsonby, A.-L., Wake, M., Tang, M.L.K., Dharmage, S.C., Allen, K.J., 2011. Prevalence of challenge-proven IgE-mediated food allergy using population-based sampling and predetermined challenge criteria in infants. *J. Allergy Clin. Immunol.* 127, 668–676.
- Pastorello, E.A., Farioli, L., Conti, A., Pravettoni, V., Bonomi, S., Iametti, S., Fortunato, D., Scibilia, J., Bindslev-Jensen, C., Ballmer-Weber, B., Robino, A.M., Ortolani, C., 2007. Wheat IgE-mediated food allergy in European patients: α -amylase inhibitors, lipid transfer proteins and low-molecular-weight glutenins. Allergenic molecules recognized by double-blind, placebo-controlled food challenge. *Int. Arch. Allergy Immunol.* 144, 10–22.
- Patriarca, G., Bonomo, A., Roncallo, C., Del Ninno, M., Pollastrini, E., Milani, A., De Pasquale, T., Gasbarrini, G., Schiavino, D., Nucera, E., 2002. Oral desensitization in cow milk allergy: immunological findings. *Int. J. Immunopath. Pharm.* 15, 53–58.
- Patriarca, G., Nucera, E., Pollastrini, E., De Pasquale, T., Lombardo, C., Bonomo, A., Roncallo, C., Pecora, V., Musumerci, S., Altomonte, G., Alonzi, C., Schiavino, D., Gasbarrini, G., 2006. Oral rush desensitization in peanut allergy: a case report. *Digest. Diseases Sci.* 51, 471–473.
- Peeters, K.A.B.M., Koppelman, S.J., van Hoffen, E., van der Tas, C.W.H., den Hartog Jager, C.F., Penninks, A.H., Hefle, S.L., Bruijnzeel-Koomen, C.A., Knol, E.F., Knulst, A.C., 2007. Does skin prick test reactivity to purified allergens correlate with clinical severity of peanut allergy? *Clin. Exp. Allergy* 37, 108–115.
- Perry, T.T., Matsui, E.C., Conover-Walker, M.K., Wood, R.A., 2004. Risk of oral food challenges. *J. Allergy Clin. Immunol.* 114, 1164–1168.
- Rancé, F., Dutau, G., Abbal, M., 2000. Mustard allergy in children. *Allergy* 55, 496–500.
- Remington, B.C., Baumert, J.L., Marx, D.B., Taylor, S.L., 2013. Quantitative risk assessment of foods containing peanut advisory labeling. *Food Chem. Toxicol.* 62, 179–187.
- Rimbaud, L., Heraud, F., LaVieille, S., Leblanc, J.-C., Crepet, A., 2010. Quantitative risk assessment relating to adventitious presence of allergens in food: a probabilistic model applied to peanut in chocolate. *Risk Analysis* 30, 7–19.
- Robertson, O.N., Hourihane, J.O'B., Remington, B.C., Baumert, J.L., Taylor, S.L., 2013. Survey of peanut levels in selected Irish food products bearing peanut allergen advisory labels. *Food Addit. Contam.: Part A* 30, 1467–1472.
- Rosenthal, E., Schlesinger, Y., Birnbaum, Y., Goldstein, R., Benderly, A., Freier, S., 1991. Intolerance to casein hydrolysate formula. *Acta Paediatr. Scand.* 80, 958–960.
- Saylor, J.D., Bahna, S.L., 1991. Anaphylaxis to casein hydrolysate formula. *J. Pediatr.* 118, 71–74.
- Scibilia, J., Pastorello, E.A., Zisa, G., Ottolenghi, A., Bindslev-Jensen, C., Pravettoni, V., Scovena, E., Robino, A., Ortolani, C., 2006. Wheat allergy: a double-blind, placebo-controlled study in adults. *J. Allergy Clin. Immunol.* 117, 433–439.
- Shaw, J., Roberts, G., Grimshaw, K., White, S., Hourihane, J., 2008. Lupin allergy in peanut-allergic children and teenagers. *Allergy* 63, 370–373.
- Sheth, S.S., Wasserman, S., Kagan, R., Alizadehfar, R., Primeau, M.-N., Elliot, S., St. Pierre, Y., Wickett, R., Joseph, L., Harada, L., Dufresne, C., Allen, M., Allen, M., Godefroy, S.B., Clarke, A.E., 2010. Role of food labels in accidental exposures in food-allergic individuals in Canada. *Ann. Allergy Asthma Immunol.* 104, 60–65.
- Skrupak, J.M., Nash, S.D., Rowley, H., Brereton, N.H., Oh, S., Hamilton, R.G., Matsui, E.C., Burks, A.W., Wood, R.A., 2008. A randomized, double-blind, placebo-controlled study of milk oral immunotherapy for cow's milk allergy. *J. Allergy Clin. Immunol.* 122, 1154–1160.
- Spanjersberg, M.Q.L., Kruijsing, A.G., Rennen, M.A.J., Houben, G.F., 2007. Risk assessment and food allergy: the probabilistic model applied to allergens. *Food Chem. Toxicol.* 45, 49–54.
- Spanjersberg, M.Q.L., Knulst, A.C., Kruijsing, A.G., Van Duijn, G., Houben, G.F., 2010. Concentrations of undeclared allergens in food products can reach levels that are relevant for public health. *Food Addit. Contam.* 27, 169–174.
- Staden, U., Rolinck-Werninghaus, C., Brewe, F., Wahn, U., Niggemann, B., Beyer, K., 2007. Specific oral tolerance induction in food allergy in children: efficacy and clinical patterns of reaction. *Allergy* 62, 1261–1269.
- Taylor, S.L., Hefle, S.L., Bindslev-Jensen, C., Bock, S.A., Burks Jr., A.W., Christie, L., Hill, D.J., Host, A., Hourihane, J.O'B., Lack, G., Metcalfe, D.D., Moneret-Vautrin, D.A., Vadas, P.A., Rance, F., Skrypec, D.J., Trautman, T.A., Yman, I.M., Zeiger, R.S., 2002. Factors affecting the determination of threshold doses for allergenic foods: how much is too much? *J. Allergy Clin. Immunol.* 109, 24–30.
- Taylor, S.L., Crevel, R.W.R., Sheffield, D., Kabourek, J., Baumert, J., 2009. Threshold dose for peanut: risk characterization based upon published results from challenges of peanut-allergic individuals. *Food Chem. Toxicol.* 47, 1198–1204.
- Taylor, S.L., Moneret-Vautrin, D.A., Crevel, R.W.R., Sheffield, D., Morisset, M., Dumont, P., Remington, B.C., Baumert, J.L., 2010. Threshold dose for peanut: risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. *Food Chem. Toxicol.* 48, 814–819.
- Turner, P., Kemp, A., Campbell, D., 2011. Advisory food labels: consumers with allergies need more than "traces" of information. *Br. Med. J.* 343, d6180–d6182.
- Unsel, M., Sin, A.Z., Ardeniz, O., Erdem, N., Ersoy, R., Gulbahar, O., Mete, N., Kokuludag, A., 2007. New onset egg allergy in an adult. *J. Invest. Allergol. Clin. Immunol.* 17, 55–58.
- Wainstein, B.K., Studdert, J., Ziegler, M., Ziegler, J.B., 2010. Prediction of anaphylaxis during peanut food challenge: usefulness of the peanut skin prick test (SPT) and specific IgE level. *Ped. Allergy Immunol.* 21, 603–611.
- Wensing, M., Penninks, A.H., Hefle, S.L., Koppelman, S.J., Bruijnzeel-Koomen, C.A.F.M., Knulst, A.C., 2002a. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. *J. Allergy Clin. Immunol.* 110, 915–920.
- Wensing, M., Penninks, A.H., Hefle, S.L., Akkerdaas, J.H., van Ree, R., Koppelman, S.J., Bruijnzeel-Koomen, C.A., Knulst, A.C., 2002b. The range of minimum provoking doses in hazelnut-allergic patients as determined by double-blind, placebo-controlled food challenges. *Clin. Exp. Allergy* 32, 1757–1762.
- Zeiger, R.S., Sampson, H.A., Bock, S.A., Burks Jr., A.W., Harden, K., Noone, S., Martin, D., Leung, S., Wilson, G., 1999. Soy allergy in infants and children with IgE-associated cow's milk allergy. *J. Pediatr.* 134, 614–622.
- Zurzolo, G.A., Koplin, J.J., Mathai, M.L., Taylor, S.L., Tey, D., Allen, K.J., 2013. Foods with precautionary allergen labeling in Australia rarely contain detectable allergen. *J. Allergy Clin. Immunol. In Practice* 1, 401–403.