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ABSTRACT

Clinical records of 286 consecutive patients reacting positively with objective symptoms to double-blind, placebo-controlled oral peanut challenges at University Hospital, Nancy, France were examined for individual No Observed Adverse Effect Levels (NOAELs) and Lowest Observed Adverse Effect Levels (LOAELs). After fitting to a log-normal probability distribution model, the ED_{10} and ED_{05} were 14.4 and 7.3 mg (expressed as whole peanut), respectively, with 95% lower confidence intervals of 10.7 and 5.2 mg, respectively. Compared to results from a previous study where the ED_{10} was based upon individual peanut thresholds gleaned from 12 publications, a statistically significant difference was observed between the ED_{50}'s, but not the ED_{10}'s of the two probability distribution curves. The Nancy patient group contains more sensitive subjects than the group from the published literature thus contributing to the observed differences. Minimum eliciting dose-distributions for patients with histories of more severe reactions (grade 4 or 5; 40 subjects) did not differ significantly from those of patients with histories of less severe reactions (grades 1–3; 123 subjects). These data and this modeling approach could be used to establish population thresholds for peanut-allergic consumers and thereby provide a sound basis for allergen control measures in the food industry.

1. Introduction

Allergic reactions to peanut are among the most prevalent and severe of all food allergies (Hourihane et al., 2007; Bock et al., 2007; Yunginger et al., 1988). The inadvertent ingestion of peanut by peanut-allergic individuals is the leading cause of fatal food-allergic reactions (Bock et al., 2007; Yunginger et al., 1988). It has also been reported that exposure to trace amounts of peanuts can provoke allergic reactions in some peanut-allergic individuals (Taylor et al., 2002). Thus, careful and complete avoidance of peanuts has been advised for peanut-allergic individuals (Taylor et al., 1986). Peanut-allergic consumers face increasingly restricted food choices in complying with this advice due, in part, to the proliferation of advisory labels such as 'may contain peanuts' (Hefle et al., 2007).

Experience with clinical oral challenge trials indicates that exposures do exist below which individuals with confirmed peanut allergy will not experience allergic reactions (Taylor et al., 2002). An individual's elicitation threshold lies between the No Observed

Adverse Effect Level (NOAEL), the highest dose that will not produce any adverse effect in that person and the Lowest Observed Adverse Effect Level (LOAEL), the lowest dose that produces an adverse effect (Taylor et al., 2009). The range of LOAEL doses for peanut-allergic individuals in clinical challenge trials spans 4–5 orders of magnitude – 0.5 mg up to 8000–10,000 mg of whole peanut (Taylor et al., 2009). The population threshold is defined as the largest amount of peanut that would not cause an adverse reaction in any individual within the total population of peanut-allergic individuals. But, of course, it is impossible to perform challenge tests on the entire peanut-allergic population, so population threshold estimates must be obtained from clinical food challenge trials conducted on defined groups of peanut-allergic individuals. The accuracy of those population threshold estimates will depend upon the representativeness of the selected population and the statistical approach used to model the distribution of the individual threshold doses from the clinical studies.

The US Food and Drug Administration has indicated that statistically-based risk assessment (including statistical techniques such as dose-distribution modeling) provides the ideal approach to the establishment of a population threshold for allergenic foods including peanut (Threshold Working Group, 2008). Taylor et al.

(2009) used dose-distribution modeling to estimate the population threshold from individual threshold information for 185 peanut-allergic subjects obtained from 12 published clinical studies. From the NOAELs and LOAELs of these patients, a dose-distribution model was constructed using interval-censoring survival analysis (Taylor et al., 2009). An ED_{10} (the dose predicted to provoke a reaction 10% of the peanut-allergic population) of 8.4 mg of whole peanut was derived based on fitting the data to a log-normal distribution. In that study, the choice of the probability distribution model had little effect on the ED_{10} estimate. While that dataset was the largest on individual peanut thresholds assembled to date, the sufficiency of these data to establish a population threshold as a basis for risk management could be questioned. First, these data were obtained from 12 different published studies using various clinical challenge protocols. In particular, the use of different challenge doses in the various protocols created a large number of NOAEL/LOAEL intervals. Furthermore, the LOAEL dose could not be defined in 67/185 subjects which increases the uncertainty about the "true" population threshold dose (Taylor et al., 2009). Secondly, patient selection biases likely existed in these published studies since there was no evidence to suggest that the peanut-allergic subjects had been randomly selected. Furthermore, the NOAEL/LOAEL intervals could only be discerned for a fraction of the total number of peanut-allergic subjects included in these published studies which likely introduces additional bias (Taylor et al., 2009). However, there is strength in that analysis because the data come from a combination of 12 studies.

This risk assessment effort (Taylor et al., 2009) demonstrated that sufficient data exist for peanut to establish an estimate of a population threshold that could be used for regulatory and food industry action/management levels. However, because of the uncertainties noted above, a similar analysis based on data obtained from group(s) of peanut-allergic subjects where a consistent challenge protocol was used and where the patient population could be adequately characterized and selection biases could be minimized, or at least better understood would be important in establishing a better estimate of the population threshold. We describe the analysis of a large clinical dataset from University Hospital, Nancy, France where diagnostic peanut challenges had been conducted on all prospective peanut-allergic patients at that clinic using a consistent challenge protocol over a period of more than 10 years.

2. Patients

Patients (286, 162 males, <1–48 years of age (median 7.0 years)) were selected for diagnostic oral, double-blind, placebo-controlled peanut challenges (DBPCFC) at University Hospital, Nancy, France based upon either a history of possible previous allergic reactions to peanut, including anaphylactic shock, or sensitization to peanuts detected at an early age but no history of actual allergic reactions to peanuts as a result of being placed on a systematic avoidance diet. Apart from being peanut-allergic, they were unselected, consecutive patients who attended the clinic as part of the treatment of their allergy. Consecutive patients include all of the patients that self-selected to seek medical diagnosis of their peanut allergy at the Nancy France clinic and were enrolled in a low-dose food challenge (patients were not randomly selected for challenge). Although a proportion of patients received more than one peanut challenge over time, the data used here are from only the initial diagnostic challenge procedure.

3. Methods

DBPCFCs were conducted in a manner consistent with the consensus clinical protocol for threshold studies (Taylor et al., 2004). Anti-histamine treatment was stopped 7 days before challenge and inhaled corticosteroids and beta agonists were stopped 24 h before challenge. Patients were not challenged while, or within a week of suffering respiratory infections or rhinopharyngitis. DBPCFC was conducted on each subject using various doses of crushed roasted peanut in apple sauce (Moner-et-Vautrin et al., 1995). An interval of 15 min was used between increasing doses of peanut. In general, one or two of three series of dosage progressions were used depending upon the described severity of historical reactions to peanut and the age of the patient (Table 1). Thus some patients started with Progression 1 while others started with Progression 2 depending on the physician's judgment about their potential reactivity. Occasionally, modifications of the progression were used instead. Both subjective and objective symptoms were recorded and generally, challenges were continued until objective symptoms were encountered or until the highest dose (7110 mg cumulative dose) had been consumed. Objective symptoms included any symptom that would have been discernable to clinical observers e.g. vomiting, urticaria, rash, angioedema, etc. Abdominal pain was considered an objective reaction only in children who did not experience symptoms in the placebo arm of the DBPCFC. Additionally, the abdominal pain should have lasted for more than 30 min or should have been of sufficient intensity to require treatment (gluco-corticoid and H1 anti-histamine) to be considered an objective endpoint symptom. Crying; prostration; mood changes (grumbling child); pharyngeal, oral, or laryngeal pruritis; nausea; or palor were minor criteria that were used to support the abdominal pain symptom. Abdominal pain as the sole symptom was not considered an objective endpoint symptom in adult subjects. Adult subjects continued with the challenge until objective symptoms were experienced.

Occasionally, the next higher dose was administered at the physician's discretion in situations where the initial reaction was very mild and transitory. Individual NOAELs and LOAELs were recorded for each peanut-allergic patient based upon the cumulative dose eliciting the initial objective reaction. In the instances where very mild and transitory reactions were observed and the next higher dose was administered, the LOAEL was considered the cumulative dose where lasting objective reactions occurred and the NOAEL was considered the previous cumulative dose. If no adverse reaction was encountered at the highest dose in Progression 3, then the patient was not considered as peanut-allergic and was not included in the dataset.

The records of peanut-allergic patients were also screened for evidence concerning the history of severity of allergic reactions occurring to peanut before DBPCFC. Patients were identified as having a previous severe reaction if they gave a history of a Severity Grade 4 or 5 reaction (objective reactions occurring in three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension) (Astier et al., 2006). Other patients were identified as having a previous non-severe reaction if they gave a history of a Severity Grade 1–3 reaction (objective symptoms occurring in 1–2 organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, angioedema but not laryngeal edema, and/or asthma not requiring treatment).

Individual NOAELs and LOAELs for all peanut-allergic patients challenged over a 17-year period from 1991 to 2008 were analyzed by an Interval-Censoring Survival Analysis (ICSA) approach as previously described (Collett, 1993; Taylor et al., 2009). Data analyses and modeling were performed in SAS v9.1 (SAS Research Institute) using the procedure LIFEREG as previously described (Taylor et al., 2009). A log-normal dose-distribution model was used to estimate the ED_{10} and the ED_{05}, the doses predicted to provoke reactions in 10% and 5%, respectively, of the peanut-allergic population.

4. Results

4.1. Dose-distributions

Individual NOAELs and LOAELs based on objective symptoms for whole peanut were obtained for 286 patients over the 17-year time period. The ED_{10} and ED_{05} were 14.4 and 7.3 mg (expressed as whole peanut), respectively, with 95% lower confidence intervals of 10.7 and 5.2 mg, respectively (Table 2). Fig. 1 shows that differences were observed between the slope of the curve of the log-normal distribution model for this dataset and the distribution modeled separately from the evaluation of the individual thresholds of peanut-allergic subjects gleaned from the published clinical literature (Taylor et al., 2009). This difference is also reflected in the ED_{50} values (the dose predicted to provoke reactions in 50% of the peanut-allergic population) which were 1036 mg of whole peanut for publications dataset and 157 mg of whole peanut for the Nancy patient dataset. Since the 185 peanut-allergic subjects included in the original analysis of the individual thresholds of peanut-allergic subjects from the published literature included 21 subjects reported by the clinical group in Nancy, France (Taylor et al., 2009), those data points were removed before the dose-distribution modeling shown in Fig. 1 – an analysis of the remaining

Table 1
DBPCFC dose progression series.

Progression 1		Progression 2		Progression 3	
Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose
0.1	0.1	5.0	5.0	10.0	10.0
0.3	0.4	10.0	15.0	100.0	110.0
1.0	1.4	50.0	65.0	500.0	610.0
3.0	4.4	150.0	215.0	1500.0	2110.0
10.0	14.4	285.0	500.0	5000.0	7110.0
30.0	44.4	465.0	965.0		

All values reported in milligram whole peanut.

Table 2
ED_{10} and ED_{05} doses for whole peanut as assessed by the log-normal probability distribution models.

| Source	Total no. of peanut-allergic individuals	ED_{10}	95% CI	ED_{05}	95% CI
Nancy data	286	14.4	10.7, 19.6	7.3	5.2, 10.4
Published papers[a]	164	14.1	6.6, 29.9	4.2	1.7, 10.1
Combined	450	12.3	9.0, 16.8	5.2	3.6, 7.4

All values reported in mg of whole peanut.

[a] Nine published studies yielded NOAELs and LOAELs for 164 peanut-allergic individuals. Twenty-one individuals from three papers (A, B, and D; see Taylor et al., 2009) were excluded from analysis to avoid potential duplication of individuals as these studies included individuals from the Nancy clinic.

164 subjects. The ED_{10} and ED_{05} of these two datasets and the combined dataset of 450 peanut-allergic subjects are presented in Table 2. The removal of the 21 Nancy patients from the original dataset caused the ED_{10} to increase from 8.4 to 14.1 mg because many of these subjects were among the most sensitive in that dataset. Four of these 21 subjects were left-censored individuals that reacted upon ingestion of the first dose (5 mg of whole peanut) in the challenge. The left-censored subjects have a profound effect in lowering the overall population threshold and, by taking these individuals out of the publications dataset, the overall ED_{10} estimate increased. This clearly shows the importance of designing low-dose challenge studies so that all individuals are interval-censored (have established NOAEL and LOAEL values). The ED_{10} and

ED_{05} from this Nancy dataset are slightly higher than the estimates obtained from the evaluation of individual thresholds gleaned from the published literature (Table 2). From the combined dataset of 450 peanut-allergic subjects, the ED_{10} and ED_{05} were 12.3 and 5.2 mg (expressed as whole peanut), respectively, with 95% lower confidence intervals for the ED_{10} and ED_{05} of 9.0 and 3.6 mg, respectively (Table 2). The slight decrease in the ED_{10} and ED_{05} values in the combined dataset compared to the Nancy dataset can be attributed to the inclusion of three very sensitive interval-censored subjects (LOAEL values ranging from 0.5 to 1.6 mg) and five left-censored individuals from the publications dataset (164 total subjects) that, when analyzed with the more sensitive subjects in the Nancy dataset, further decreases the ED_{10} and ED_{05} values for the combined dataset. The estimates from the combined dataset and the Nancy dataset, however, are not significantly different.

4.2. Responses to challenge

Many of the subjects experienced multiple symptoms during the oral challenge. All of these symptoms are summarized in Table 3, both overall and according to dose progression, to which they had been allocated according to the physician's initial view of likely reactivity. Thus individuals who were thought likely to react at very low doses were started at 0.1 mg and challenged up to 44.4 mg. This ensured that an individual NOAEL was obtained for all but eight subjects. Almost all symptoms observed during challenges in all groups were mild. Adult subjects who experienced abdominal pain as their only initial symptom were continued in the oral challenge until objective symptoms were observed. In all cases, more severe
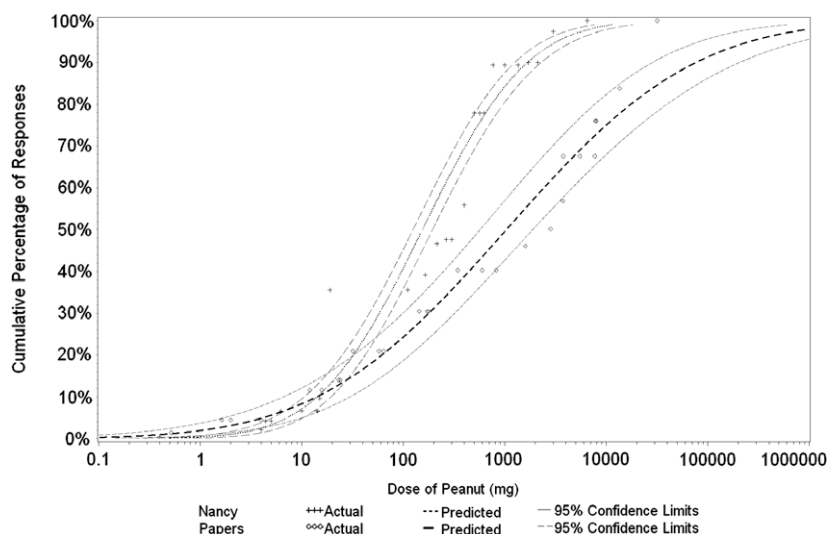
Fig. 1. Log-normal probability distribution models of individual peanut thresholds (expressed as whole peanut) for peanut-allergic individuals gleaned from publications and compiled from diagnostic challenge trials in Nancy, France.

Table 3
Summary of symptoms[*] reported on challenge for 286 peanut-allergic individuals.

Symptoms	Progression 1		Progression 2		Progression 3		Total	
	Number of reactions	%	Number of reactions	%	Number of reactions	%	Number of reactions	%
Conjunctivitis	3	5	27	14	5	14	35	12
Rhinitis	2	3	29	15	5	14	36	13
Hives	5	9	34	18	18	50	57	20
Angioedema	3	5	13	7	5	14	21	7
Rash or eczema	2	3	14	7	7	19	23	8
Sibilant rales (wheeze)[a]	2	3	24	13	6	17	32	11
Decrease PEF (20%)	0	0	22	11	4	11	26	9
Asthma	2	3	27	14	4	11	33	12
Tachycardia	0	0	11	6	5	14	16	6
Fall of BP	0	0	4	2	1	3	5	2
Vomiting	6	10	57	30	4	11	67	23
Abdominal pain (+ other symptoms)	30	52	117	61	17	47	164	57
Abdominal pain only	17	29	32	17	4	11	53	19
Diarrhea	4	7	12	6	2	6	18	6
Other objective symptoms	3	5	34	18	7	19	44	15
Subjective symptoms	15	26	66	34	10	28	91	32
Total number of peanut-allergic individuals	58		192		36		286	
Males	37		106		19		162	
Females	21		86		17		124	
Age (years) (median; range)	7.5	2.9–25	7.0	<1–48	5.5	1.4–22	7.0	<1–48

[*] Many subjects experienced multiple symptoms during the double-blind, placebo-controlled food challenge (DBPCFC). All symptoms were recorded according to the dose progression where the reactions occurred and total number of reactions for each symptom is provided.

[a] Sibilant rales (wheeze) are heard by auscultation and are the first sign of asthma crisis. Asthma was used only to describe when a subject was dyspnoeic.

objective symptoms such as vomiting or diarrhea occurred upon ingestion of increasing doses. A similar observation was also made by Ballmer-Weber et al. (2007) where 5 soy-allergic subjects with initial abdominal pain reacted with objective symptoms upon increasing the dose. More severe symptoms, such as a fall in blood pressure, were only observed occasionally, while they were never observed during Progression 1 (low dose). Interestingly, the symptoms experienced by those who reacted to the first (low dose) progression showed, if anything, somewhat milder symptoms than the other two groups. The most common symptoms were linked to the gastrointestinal tract, namely abdominal pain (includes those experiencing abdominal pain only and abdominal pain plus other symptoms) and vomiting, which were experienced by approximately 76% and 23% of patients, respectively.

4.3. Severity by history vs. reactive dose

Among the 286 peanut-allergic patients from Nancy, 163 subjects had experienced a reaction prior to challenge and information was available on the severity of those reactions. A total of 40 subjects were identified who had previously experienced severe reactions (Severity Grade 4 or 5) before the DBPCFC compared to 123 subjects who had experienced less severe reactions (Severity Grade 1–3). The threshold distribution of patients with histories of more severe reactions did not differ significantly from the threshold distributions from patients with histories of less severe reactions (data not shown). The ED_{10}'s for the two groups were quite similar (Table 4). In contrast, the ED_{10} for the remaining 123 patients, most of who did not present initially with a history of an allergic reaction to peanut was somewhat higher, although this difference was not statistically significant (Table 4). Previous oral exposure to peanut is uncertain in this group.

5. Discussion

Thresholds are needed to assess the risk posed by residues of allergenic foods particularly at the population level and to determine appropriate risk management strategies. Population thresholds are critical to the assessment of public health risk, the development of appropriate risk management approaches, and the establishment of regulatory safeguards for allergic consumers. Dose-distribution probability modeling has been identified as a promising approach to estimate population thresholds (Bindslev-Jensen et al., 2002; Crevel et al., 2007). While the US Food and Drug Administration indicated that such modeling would provide the ideal approach to the establishment of population thresholds for allergenic foods including peanut (Threshold Working Group, 2008), they have questioned whether enough data exist for such modeling. Recently, we demonstrated that sufficient data could be gleaned from the published literature for peanut to estimate doses predicted to elicit (mild) reactions (Perry et al., 2004) in 10% of the at-risk population with reasonable precision (Taylor et al., 2009).

We have now confirmed and strengthened our initial estimate of the population threshold for peanut. Individual NOAELs and LOAELs were found, respectively, for 278 and 286 peanut-allergic subjects by screening the records of University Hospital,

Table 4
ED_{10} doses[*] for whole peanut as assessed by the log-normal probability distribution model for Severity Grade.

Severity grade	Total no. of peanut-allergic individuals	ED_{10}	95% CI
Severe[a]	40	10.4	4.8, 22.6
Non-severe[b]	123	10.2	6.4, 16.1
No prior history[c]	123	27.0	17.4, 42.0

All values reported in mg whole peanut.

[*] Statistically valid ED_{05} estimates could not be provided due to the limited number of subjects in all of the severity grade classes.

[a] Severe reactions include three organ systems, asthma requiring treatment, laryngeal edema, and/or hypotension.

[b] Non-severe reactions include one or two organ systems, abdominal pain, rhinoconjunctivitis, urticaria, eczema, non-laryngeal angioedema, and/or mild asthma (peak flow rate <80%).

[c] History of prior allergic reactions and severity of reactions were not available. These individuals were identified as being sensitized to peanut by means of diagnostic tests.

Nancy, France. The ED_{10} (14.4 mg of whole peanut) obtained from this dataset is in reasonable agreement with the earlier estimate (8.4 mg) by the log-normal distribution model. When the 21 subjects from the Nancy clinic were removed from the earlier dataset to avoid possible duplications, the ED_{10} increased to 14.1 mg. These 21 subjects were among the most sensitive and included four left-censored subjects in the earlier dataset accounting for the difference. Some patient selection bias is obvious because the NOAELs and LOAELs of only the 10 most sensitive of 103 peanut-allergic patients could be discerned from one of those earlier Nancy publications (Morisset et al., 2003; Taylor et al., 2009). Furthermore, combining the two datasets allowed the estimation of the ED_{10} and the ED_{05} based on the NOAELs and LOAELs of 450 peanut-allergic subjects with a higher level of confidence. While the ED_{10}'s for the two datasets are quite similar, the dose-distribution curves are strikingly different as reflected in Fig. 1 and by the ED_{50}'s. The difference indicates that the Nancy dataset is weighted toward more sensitive peanut-allergic subjects.

The data on NOAELs and LOAELs from the Nancy patients offer some distinct advantages in comparison to the use of the information from the published literature. Population thresholds should ideally be based upon clinical data obtained from a representative sample of the entire peanut-allergic population. The published studies examined for our earlier population threshold estimate (Taylor et al., 2009) involved selected patients and were highly heterogeneous. NOAELs and LOAELs could only be identified or discerned for a proportion of the total number of subjects from some publications considered in the earlier study (Taylor et al., 2009). In contrast, the Nancy subjects were 286 consecutive patients with positive peanut challenges. The patient selection bias is thus reduced although the subjects do self-select to seek the medical diagnosis of their peanut allergy. Furthermore, the Nancy challenge protocol with three dosing progressions enhances the likelihood that the dosage range will encompass both the NOAEL and LOAEL. In fact, no right-censored subjects (LOAEL > highest challenge dose) were encountered in the Nancy group (such subjects would have been considered not to be peanut-allergic), while 67 such individuals were included among the 185 subjects in the earlier analysis (Taylor et al., 2009). The number of left-censored subjects (LOAEL = lowest challenge dose) was similar in the Nancy group (eight left-censored subjects) and the published studies group (nine left-censored individuals) (Taylor et al., 2009). Subsequently, we have re-analyzed the dose-distributions from the publications dataset with and without inclusion of the right-censored subjects (Table 5). The ED_{10} is slightly lower for the distribution without any right-censored subjects (6.1 mg of whole peanut) by comparison to the group that contains the 67 right-censored subjects (14.1 mg of whole peanut). Typically, clinical challenge trials

are limited to several hours, leading to practical limitations in designing experiments that would ensure the identification of both NOAELs and LOAELs for all subjects. Thus, the use of the three dosage progressions in the Nancy clinic allowed determination of the individual NOAELs and LOAELs for all peanut-allergic subjects.

Another uncertainty regarding the development of population thresholds for peanut is the possible exclusion of patients with histories of severe reactions from clinical challenge trials (Taylor et al., 2002). Without studies on patients with histories of severe reactions, the possibility exists of a more sensitive sub-population, which might remain unprotected if risk management was based on the response of the less sensitive majority. In the previous estimate of the population threshold for peanut (Taylor et al., 2009), the selection of patients and the severity of the symptoms involved in their previous reactions was impossible to determine. However, in the Nancy group, patients with previous histories of severe reactions, including anaphylactic shock, were not excluded from the diagnostic challenges. Of 163 challenged patients with known previous histories of allergic reactions to peanut, 40 subjects had histories of severe reactions. But, as shown in Table 4, the ED_{10} for the severe reactors was essentially the same as that of the non-severe reactors. Thus, subjects with histories of severe allergic reactions to peanuts do not appear to represent a distinct sub-population with greater sensitivity. Interestingly, the ED_{10} for the remaining 123 subjects, most of whom had no history of previous reactions to peanuts, was higher. However, the eliciting doses for this group were still sufficiently low to indicate that they would be at risk from the ingestion of peanut. When setting action levels for regulatory purposes, the key criterion is safety. While it is impossible to be sure of protecting every single allergic individual against a reaction, it is important to demonstrate that, in the event of inadvertent exposure, any reaction will be mild. The data on the most sensitive individuals, namely those who reacted to the lowest amounts of peanut offer considerable reassurance in this respect, since all of them showed mild symptoms at the doses which elicited reactions (Table 3).

Using the combined dataset of 450 peanut-allergic individuals allows prediction of the ED_{10} and ED_{05} with a high level of confidence. In our opinion, these data should be considered for use by regulatory and public health authorities in the establishment of population thresholds for peanut. Data should also be gathered on individual NOAELs and LOAELs for other commonly allergenic foods to determine if their threshold levels are similar to peanut. However, lesser amounts of data are likely available than for peanut.

Conflict of Interest

The authors declare that there are no conflicts of interest.

Acknowledgments

Table 5
ED_{10} and ED_{05} doses for whole peanut as assessed by the log-normal probability distribution model for inclusion of the right-censored subjects in the publications dataset.

Group	Total no. of peanut-allergic individuals	ED_{10}	95% CI	ED_{05}	95% CI
Right-censored[a]	164	14.1	6.6, 29.9	4.2	1.7, 10.1
Non-right-censored[b]	97	6.1	2.8, 13.2	2.2	0.9, 5.4

All values reported in mg of whole peanut.

[a] Nine published studies yielded NOAELs and LOAELs for 164 peanut-allergic individuals, 67 of which were right-censored (see Taylor et al., 2009).

[b] Non-right-censored dataset contains NOAELs and LOAELs for 97 peanut-allergic individuals from the published studies that are either left-censored or interval-censored.

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