

Threshold dose distribution for cashew nut allergy in children

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To the Editor,

Allergy to cashew nut in children is increasingly recognized in clinical practice, and the prevalence of this allergy seems to increase. Furthermore, previous studies showed the potential for cashew nut to cause anaphylaxis.¹

Despite the increasing prevalence of cashew nut allergy and the severity of the reaction to this allergen, there are only few studies on this allergy, especially on the threshold dose. Defining food allergen threshold is an important tool and benefits multiple sectors of society: food allergic individuals, their caretakers, the food industry, policymakers and government officials.² Knowledge of threshold doses is necessary for clinical management but also for informing policy on precautionary labelling.³ Acceptance of management thresholds by regulatory authorities could benefit allergic consumers as there would be more transparency in the use of advisory labelling.⁴

The aim of our study was to determine threshold distribution dose in children with cashew nut allergy. All children who underwent an oral food challenge (OFC) to cashew nut at the Pediatric Allergology Department of the University Hospital of Nancy between November 2013 and August 2015 were included. All children with negative OFCs to more than 1980 mg of cashew nut protein were excluded and considered as non-allergic. Having a history of severe reactions was not an exclusion criterion for OFC. OFC was performed as a routine diagnostic test for suspected allergy to cashew nut on skin sensitization or for threshold evaluation in children known to be allergic to cashew nut. After having been informed by the physician, all parents gave their written consent for the performance of OFCs and the use of data. The clinical database was declared to the French Data Protection Authority under number R2016-11.

The different progressions used for OFCs are described in Table 1 and are similar to those described by Taylor et al.⁵ The

doses of cashew nut were spaced at 20-40 minutes and given in powder form in applesauce. Most of the time, we performed open OFC rather than double-blind placebo-controlled OFC because of time limitations. OFC was considered as positive in case of objective symptoms as described by Sampson et al⁶ or in case of a severe abdominal pain persistent more than 40 minutes. Double-blind placebo-controlled OFC was used in case of subjective symptoms in previous challenge. We scored the severity of the reaction according to Astier's classification.⁷ A dose distribution model was constructed using interval-censoring survival analysis.⁵ Children with a negative or doubtful OFC to less than 1980 mg of cashew nut protein were treated as right censored. Stepwise backward selection procedures were used to retain significant factors (at a 20% threshold in bivariate analyses and 5% in multivariate analyses). Three models (Weibull, Log-Normal and Log-Logistic) were used to estimate the eliciting doses ED₀₅, ED₁₀ and ED₅₀, the dose predicted to provoke reactions in 5%, 10% and 50% respectively, in our cashew nut-allergic population.

Among the 141 children who underwent OFC to cashew nut, 33 were non-allergic children and were excluded. Among the remaining 108 children, 52 had a positive OFC to cashew nut and 56 had an incomplete evaluation and were right censored.

Threshold doses were obtained for 52 children aged from 2 to 14 years old with a median age of 7 years old. There was a slight predominance of boys (57.7%). Atopic characteristics were the following: atopic dermatitis (73.1%), asthma (44.2%), rhinoconjunctivitis (32.7%), polysensitization (84.6%) and other food allergies (65.4%). Prior history of allergic reaction to cashew nut was found in 21 children (40.4%). Size of skin prick test to raw cashew nut was ranged from 4 to 32.5 mm (median 9.8 mm), and specific IgE levels to cashew nut were ranged from 0.14 to 209 kU/L (median 3.3 kU/L). In the right censored group, there was a higher percentage of boys ($P = .03$), a lower prevalence of atopic dermatitis ($P = .02$), a slightly

lower size of skin prick test ($P = .04$) but more children with other food allergies ($P < .0001$).

The severity of the allergic reaction after the OFC was grade 3 or 4 according to Astier's classification for 48.1% of the children. No grade 5 reactions occurred.

Individual threshold doses ranged from 0.8 to 2970 mg of cashew nut proteins. Prior history of allergic reaction and severity of the reaction were not associated with the threshold dose (respective P -value at 0.24 and 1). Among the 52 children with a positive OFC to cashew nut, there was no significant correlation between the size of SPT and the eliciting doses ($P = .10$) neither between sIgE to cashew nut and eliciting doses ($P = .31$). The threshold dose distribution curves according to Weibull, Log-Normal and Log-Logistic models are shown in Figure 1.

According to the Log-likelihood value, the best-fitted model is the Weibull with the right censored of the 56 children with an incomplete evaluation. According to this model, the ED_{05} , ED_{10} and ED_{50} and their 95% confidence intervals were, respectively, 0.9 mg [0; 3.5]; 2.8 mg [0; 9.7] and 57.3 mg [15.0; 216.2] of cashew nut proteins.

Thresholds constitute a critical piece of information in assessing the risk from allergenic foods at both individual and population

levels. Our French paediatric single-centre study shows that threshold doses for cashew nut in children are low with an ED_{05} close to 1 mg of protein.

Compared to the study of Blom et al,⁸ we found slightly higher EDs than those for any type of symptoms but lower EDs than those for objective symptoms. In our study, we have a higher proportion of children with objective symptoms (92.3%) than in Blom's study (49%). Nevertheless, the ED_{05} in our study (0.9 mg) is markedly lower than the objective ED_{05} found by Blom et al (7.4 mg). Differences in the incremental scales, in the preparation and matrix of the doses and in atopic comorbidities may explain this gap between the ED_{05} .

Our results reinforce those found by Van der Valk et al⁹ with low ED_{05} (0.8–1.6 mg) and ED_{10} (3.5–4.3 mg). However, their ED_{50} value was much higher than our (108.4–149.1 vs 38.5–57.3). This difference in ED_{50} could be explained by the use of an 8-step incremental dose regimen in Van Der Valk's study, faster than our 4 progressions on 4 separate days.

In our study, dose progressions and matrix used for OFC were the same than in the study of Taylor et al,⁵ for peanut, which made the comparison easier. Compared to this study, EDs (in mg of proteins) for cashew nut are lower than those for peanut: 0.9 vs 1.9 mg

TABLE 1 Challenge doses used in oral food challenge in mg of cashew nuts protein

	Progression 1		Progression 2		Progression 3		Progression 4	
	Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose	Dose	Cumulative dose
Dose 1	0.2	0.2	3.0	3.0	19.8	19.8	198	198
Dose 2	0.6	0.8	9.9	12.9	79.2	99	396	594
Dose 3	2.0	2.8	29.7	42.6	198	297	594	1188
Dose 4	5.9	8.7	56.4	99	396	693	792	1980
Dose 5			99	198	693	1386	990	2970

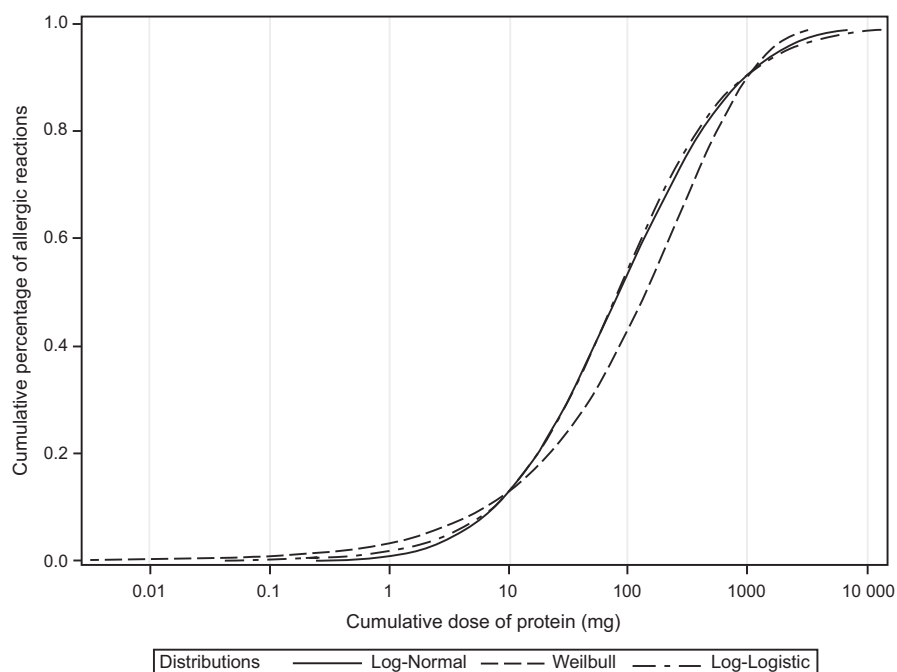


FIGURE 1 Probability distribution curves (obtained with Log-normal, Weibull and Log-logistic distribution) of threshold for cashew nut as cumulative doses in milligram of total protein

for ED₀₅ and 2.8 vs 3.7 mg for ED₁₀. These results suggest that cashew nut can cause allergic reaction with a smaller amount of proteins than peanut does.

Our study confirms that cashew nut allergy can cause severe reactions even at low doses whatever the age or the presence of prior history of allergic reactions to cashew nut. Although Glaumann et al showed that threshold dose is not reproducible in the same child,¹⁰ studying threshold dose in an allergic population allows to know the general risk of an allergy at a population level and not at an individual level. Knowing that five per cent of the allergic population can react at a dose lower than 1 mg of cashew nut protein and that almost half of the allergic children may have a reaction with at least two organs involved, is of importance for the clinical management of cashew nut allergy.

Studies on predictive factors of severe allergy to cashew nut are needed to improve the management of cashew nut allergy but also to understand better why allergy to cashew nut is so severe.

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CONFLICT OF INTERESTS

All authors declare that they do not have any competing interest as regard this article.

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