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Letter

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A previous study[1] found that 137 of 179 cashew nut sensitized children (76.5%) suspected of having cashew nut allergy had a positive double-blind, placebo-controlled food challenge (DBPCFC result), with 63 of 137 children (46%) manifesting subjective and/or objective symptoms to the lowest dose (1 mg of cashew nut protein). The primary aim of this study was to determine the distribution of threshold doses and the eliciting doses (EDs) in this population. The secondary aim was to investigate whether children who reacted to 1 mg of cashew nut (n = 63) could react to even lower doses than 1 mg (low-dose follow-up study).

The children participated in the Improvement of Diagnostic Methods for Allergy Assessment (IDEAL; trialregister.nl Identifier: NTR3572). The inclusion and exclusion criteria and detailed study protocol with stop criteria for the DBPCFC were previously described.[1] Briefly, we measured sensitization (specific IgE [sIgE] and skin prick test [SPT]) with cashew nut extract and performed DBPCFC tests with an 8-step incremental dose regimen (1, 3, 10, 30, 100, 300, 1,000, and 1,736 mg of cashew nut proteins).[2] All children who reacted to 1 mg of cashew nut in the IDEAL study were asked to participate in a low-dose follow-up study, which consisted of a DBPCFC with a 6-step incremental dose regimen, starting with 0.01 mg, followed by increasing doses of 0.03, 0.10, 0.30, 1, and 3 mg of cashew protein, performed between 4 and 30 months after the initial IDEAL challenges. The low-dose challenge results were considered positive if objective or subjective symptoms occurred. There were no stop criteria, and all patients completed the low-dose DBPCFC test to step 6, unless not medically justified or unethical or if the patient refused to continue the test. To facilitate the weighing of these small doses, ground cashew nuts were diluted 1:10 with granulated sugar, according to the technical method of Taylor et al.[3]

The Interval-Censoring Survival Analysis approach was used to analyze the no observed adverse effect level and lowest observed adverse effect level intervals for each

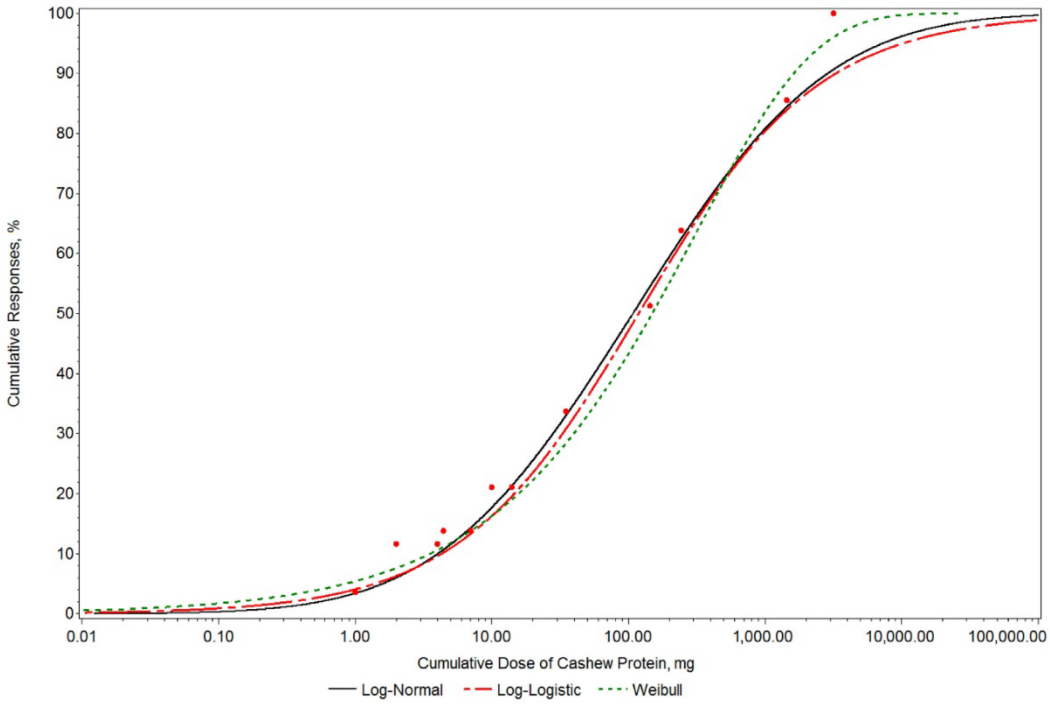
allergic individual as described previously.[4] The SAS LIFEREG procedure, version 9.2 (SAS Institute Inc, Cary, North Carolina), was used to fit the log-normal, log-logistic, and Weibull parametric distributions based on cumulative doses for this cashew allergic population, and 95% CIs were calculated. The EDs were determined.[4]

The patient characteristics and diagnostic results of the 179 participating children of the IDEAL study were previously described.[1] The median age of the children was 9.0 years (range, 2–17 years), with 106 boys (59%) and 73 girls (41%). The median sIgE cashew was 3.72 kU/L (range, 0–≥ 100 kU/L). The median histamine equivalent prick index area of cashew SPT was 3.02 (range, 0–15.16).[5] Most children experienced gastrointestinal symptoms (nausea, vomiting, stomach pain, and diarrhea) (72%), followed by oral allergy symptoms (64%), skin symptoms (redness and itchiness) (28%), angioedema (27%), and urticarial symptoms (21%). The low-dose follow-up study included 12 of 63 children (10 girls [83%]; median age, 13.0 years).

Cumulative distribution curves for the percentage objective eliciting threshold in the 137 cashew nut allergic children were measured (Fig. 1). It was not possible to calculate the threshold distribution curve for subjective symptoms because of the high percentage of children (46%) reacting to dose 1 with subjective symptoms. The doses at which 5%, 10%, or 50% of the cashew allergic population (ED_{05}, ED_{10}, and ED_{50}, respectively) would be expected to experience objective symptoms ranged from 0.8 to 1.6 mg, 3.5 to 4.3 mg, and 108.4 to 149.1 mg of cashew nut protein for the ED_{05}, ED_{10}, and ED_{50}, respectively, based on the log-normal, log-logistic, and Weibull models.

Of the 12 low-dose challenge tests, 8 results were positive, 3 were negative, and 1 was undetermined. Because only 12 children participated and 51 did not, we compared the groups to exclude selection bias (Fisher exact test, Mann-Whitney test). There was no significant difference in terms of age ($P = .83$), sIgE to cashew ($P = .46$), SPT to cashew ($P = .21$), and severity of reaction during the DBPCFC with cashew nut ($P = .75$). Only sex differed significantly ($P = .004$). The lowest dose of cashew nut protein to which subjective symptoms occurred was 0.01 mg, whereas for transient objective symptoms (red skin), this was 0.30 mg. Placebo reactions during the low-dose challenge test were reported in a higher percentage (4 of 12 children [33%]) than in the original challenge test (20 of 179 children [11%]). These 4 placebo reactions during the low-dose follow-up study were most likely caused by increased anxiety. One challenge was therefore undetermined, and the other 3 placebo reactions consisted mainly of mild oral allergy symptoms, in contrast to more severe symptoms, such as stomachache, nausea, tiredness, feeling of swollen throat, and erythema during the verum day. Consequently, there was no doubt about the positive outcome of these challenges.

Three children reacted to a higher dose of cashew nut protein, and 4 patients did not react at all in the low-dose challenge test. We could not find a relation in interval between the IDEAL study and the low-dose follow-up study (higher or lower doses reactions) as being a cause of the difference in reaction doses in both studies. Previously, Glaumann et al.[6] observed in 29 peanut allergic patients that only 2 of these children reacted to the same threshold dose and with the same severity score in 2 successive food challenge tests with peanut.



	Cumulative ED_{05}, mg of protein		Cumulative ED_{10}, mg of protein		Cumulative ED_{50}, mg of protein	
Log-Normal	1.6	(95% CI, 0.8-3.3)	4.1	(95% CI, 2.2-7.6)	108.4	(95% CI, 64.4-182.5)
Log-Logistic	1.4	(95% CI, 0.6-3.3)	4.3	(95% CI, 2.1-8.8)	118.8	(95% CI, 70.1-201.3)
Weibull	0.8	(95% CI, 0.3-2.5)	3.5	(95% CI, 1.5-8.4)	149.1	(95% CI, 93.9-236.7)

Figure 1. Cumulative distribution of objective threshold in 137 cashew nut allergic children. Distribution curves are based on no observed adverse effect levels and lowest observed adverse effect levels for objective symptoms. Data were fitted with the use of different statistical models (log-normal, log-logistic, andWeibull models). Cumulative objective eliciting doses were calculated using Interval-Censoring Survival Analysis. All doses were calculated in milligrams of cashew protein.

Concerning ED studies, the study by Blom et al.[7] found a much higher ED_{05} in 31 cashew nut allergic children at 7.4 mg of cashew nut protein compared with the ED_{05} in our study. The authors indicate in the discussion that this is an unexpectedly high quantity, taking into account that cashew nut allergy is considered to be as severe as a peanut allergy. The study by Taylor et al.[4] found in 286 peanut allergic patients an ED_{05} for objective symptoms of 7.3 mg of whole peanut (equivalent to 1.8 mg of peanut protein based on 25% protein in a peanut kernel). Our study found a lower cashew nut ED_{05} for objective symptoms than EDs for other allergens as reported in the above-mentioned study.

Minimal EDs for different allergenic foods were previously investigated by an expert panel in a study on threshold dose by Taylor et al.[8] This study found that the ED on which 1% (ED_{01}) of the population reacted with objective symptoms was 0.1 mg (log-logistic) and 0.22 mg (log-normal) for peanut. The ED_{01} ranges from 0.02 to 0.25 mg of protein for

hazelnut based on the log-normal, log-logistic, and Weibull models. The 0.30 mg of cashew nut protein as the lowest ED of mild objective symptoms in our low-dose follow-up study is in the same order of magnitude.

In conclusion, the statistically determined ED_{05} was very low (0.8–1.6 mg of cashew nut protein). Individual patients may react to as little as 0.3 and 0.01 mg of cashew nut protein with mild objective symptoms and subjective symptoms, respectively. However, the low-dose challenge tests were performed only in 12 children, they were not reproducible, and the children reported mainly subjective symptoms, which makes interpreting the low-dose data with caution necessary.

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