

Determination of no-observed-adverse-effect levels and eliciting doses in a representative group of peanut-sensitized children

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Background: Current labeling practices for allergenic foods like peanut can be inadequate. For future regulatory and industry guidelines, information on no-observed-adverse-effect levels (NOAELs) and eliciting doses (EDs) for allergenic foods is necessary.

Objective: To determine NOAEL and ED in a representative group of peanut-sensitized children, relate these data to history and sensitization, and evaluate the outcome of dietary management.

Methods: From an overall eligible group of 96 peanut-sensitized children, a representative group of 27 was evaluated by questionnaires, skin prick test, determination of specific IgE, and double-blind placebo-controlled food challenge (DBPCFC) with peanut according to the international consensus protocol, with 9 doses ranging from 10 µg to 3 g peanut flour. Dietary management was evaluated over a 12-month period.

Results: Twenty-two children (81%) had a positive DBPCFC. The NOAEL in this group was 1 mg peanut flour, corresponding to 2 mg whole peanut. The ED for subjective symptoms (10 mg to 3 g) was significantly lower than for objective symptoms (100 mg to 3 g; $P = .002$). Severe reactions occurred only at high doses. EDs were not correlated to previous reactions by history, skin prick test, or specific IgE levels. All patients with a positive DBPCFC were advised to follow a strict diet. During the follow-up period, 10 patients had a less strict diet likely containing traces of peanut. In 3 cases, a mild reaction occurred with food products labeled "may contain peanut."

Conclusion: The NOAEL in a representative group of children with peanut allergy was 2 mg. Dietary compliance in half of this group was inadequate. (*J Allergy Clin Immunol* 2006;117:448-54.)

Key words: Peanut allergy, children, double-blind placebo-controlled challenge, no-observed-adverse-effect level, eliciting dose, dietary management, food labeling

Abbreviations used

DBPCFC: Double-blind placebo-controlled food challenge
ED: Eliciting dose
IU_A/mL: International units allergen-specific IgE per milliliter
NOAEL: No-observed-adverse-effect level
OAS: Oral allergy syndrome
SPT: Skin prick test

In recent years, peanut allergy seems to be on the rise in westernized countries, with a prevalence of 1% to 1.5%.¹⁻³ Peanuts, together with tree nuts, account for the majority of food allergic reactions with fatal outcome both in children and in adults.⁴ Because spontaneous resolution of peanut allergy in children is rare⁵⁻⁷ and curative treatment is not yet available,⁸ the majority of children cope with a lifelong elimination diet. Strict elimination of peanuts is the rule because traces of peanut can cause a severe allergic reaction in sensitive subjects.⁹⁻¹¹ However, strict elimination is difficult, especially because food labeling practice can be still inadequate.^{12,13} Recent developments intending to improve regulatory aspects of food labeling have led to increased advisory labeling.^{14,15} This is beneficial with respect to the prevention of adverse reactions, but may in the same time lead to a rise in so-called "may contain" labeling of products that do not necessarily contain allergenic food residues.¹⁶ To address this problem, information on no-observed-adverse-effect levels (NOAELs) of peanut is needed. Recently, a consensus protocol for double-blind placebo-controlled food challenge (DBPCFC) aimed to determine eliciting doses (EDs) has been developed.¹⁷ This protocol also facilitates comparison of results from different centers.

This study was designed to determine a NOAEL and individual EDs in a representative group of peanut-sensitized children using the new consensus protocol and to investigate related patient factors, like history and sensitization. In addition, we evaluated the outcome of dietary management after gold standard diagnostic test during a 12-month follow-up period on the occurrence of allergic reactions in everyday life.

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METHODS

Patients

Between January 2001 and January 2003, 572 children visiting the outpatient clinic of the Department of Pediatric Dermatology and Allergology were routinely screened for peanut sensitization, which was confirmed in 267 children. Peanut elimination diets were initiated in children with a history of allergic reactions to peanut and in children without any known intake of peanut. Children older than 3.5 years with sensitization to peanut and a peanut elimination diet were considered eligible. All eligible children ($n = 96$; 67 boys and 29 girls; mean age, 7.5 years) were approached using a standardized questionnaire about previous allergic reactions to peanut. Parents of 61 children (61/96) responded, of whom 36 were interested in participating and 25 were not interested. From the 36 interested children, 27 were included in this study to evaluate peanut allergy by specific IgE measurement, skin prick test (SPT), and DBPCFC. Parents of 35 of the 96 children did not respond. Information on previous reactions to peanut in this group was obtained by telephone using the same questionnaire. Six children were lost to follow-up.

Parents of the selected study group ($n = 27$) completed an extensive questionnaire about atopy, elimination diet, and previous allergic reactions to peanut. SPT and specific IgE measurements were repeated, and a DBPCFC was performed by using the new standardized protocol¹⁷ to establish ED. Dietary management and allergic reactions to peanut were documented during a 12-month follow-up period. All parents gave written informed consent before enrollment in the study. The study was reviewed and approved by the Central Committee of Human Based Research in the Netherlands (CCMO, The Hague, The Netherlands).

Sensitization

Skin prick tests were performed on the patient's back with a standardized prick needle using commercial peanut extract (ALK-Abelló, Nieuwegein, The Netherlands). Before the skin tests, patients discontinued antihistamines for at least 2 days. Histamine dihydrochloride (10 mg/mL) was used as a positive control, and the glycerol diluent of the SPT extracts was used as a negative control (ALK-Abelló). The wheal reaction was measured after 15 minutes and transferred with transparent adhesive tape onto a record sheet. The area of the skin wheal was determined by computer scanning.¹⁸ SPT responses were standardized by dividing the wheal area of the peanut prick by that obtained for the histamine control.

Specific IgE levels were determined by using CAP system FEIA (Pharmacia Diagnostics, Uppsala, Sweden) according to the manufacturer's instructions. IgE levels of more than 0.35 international units allergen-specific IgE per milliliter (IU_A/mL) were considered positive. Besides peanut, coexisting sensitization for other allergens was investigated by CAP system FEIA. The following allergens were tested: house dust mite, grass pollen, hen's egg, birch pollen, soy, and cow's milk.

DBPCFC

Eliciting doses for peanut were investigated by DBPCFC according to the guidelines of a recently published international protocol¹⁷ with some modifications. Exclusion criteria involved the use of β -blocking agents, angiotensin-converting enzyme inhibitors, or immunosuppressive agents and any relevant disease; none of the children in this study was excluded. One medical doctor supervised all challenges in a clinical setting equipped for resuscitation and monitoring of vital signs. Before the test, children discontinued antihistamines (48 hours), β -mimetics (12 hours), and topical steroids (24 hours). Before starting the DBPCFC, a thorough clinical examination was

performed. Blood pressure, heart rate, breath sounds, abdominal palpation, and inspection of the skin using the Severity Scoring of Atopic Dermatitis Index (SCORAD)¹⁹ were all recorded. Challenge materials were prepared by the hospital pharmacy, consisting of 9 portions of defatted light roasted peanut flour: 10 μ g, 100 μ g, 500 μ g, 1 mg, 10 mg, 100 mg, 300 mg, 1 g, and 3 g (protein content 50%, fat 12% by Leco 2000 method; kindly provided by the Food Allergy Research and Resource Program, University of Nebraska). Portions of 10 μ g to 10 mg and of 100 mg to 3 g peanut flour were masked in 100 mg or 10 g whole-wheat instant cereal, respectively (a pinch of cinnamon powder was added to improve masking). Four placebos were randomly interspersed and consisted of whole-wheat instant cereal and a pinch of cinnamon. The use of interspersed placebos was chosen to complete the procedure in 1 day. Just before administering, the test meals were mixed with 1 tablespoon applesauce (in case of the low doses, 10 μ g to 10 mg peanut flour) and with 10 mL warm water with 5 tablespoons applesauce (in case of the higher doses, 100 mg to 3 g peanut flour). The doses were given in intervals of 15 minutes for the low doses and 30 minutes for the higher doses. The interval of 15 minutes (a slight modification from the protocol) was chosen for the low doses because of practical reasons to attain full cooperation of the child. In case of a reaction, the next dose was postponed until all symptoms were resolved. The challenge was discontinued when objective symptoms occurred or when consistent subjective symptoms occurred on at least 3 subsequent doses. The symptoms were treated with appropriate medication.²⁰ Reactions like the oral allergy syndrome (OAS),²¹ nausea, and abdominal pain were referred to as subjective symptoms. Objective symptoms indicative of an allergic reaction included urticaria, facial swelling, rhinoconjunctivitis, vomiting, diarrhea, dyspnea, bronchoconstriction, and tachycardia. Symptoms were graded according to the scale of Mueller²² from 0 to 4. Children with a reaction to peanut stayed in the ward for at least 4 hours after disappearance of the allergic symptoms. If no reaction occurred during the DBPCFC, the challenge was continued with an open dose of 10 g peanuts. The peanuts were fried under controlled circumstances to exclude cross-contamination with nuts. Allergenicity appeared comparable with that of roasted peanuts (data not shown). These children were kept under medical supervision for at least 2 hours after the last ingested dose. To document possible late reactions, all parents were contacted by telephone the day after the challenge.

Follow-up

At the end of each DBPCFC, dietary advice was given to the parents. After a negative DBPCFC, children were allowed to eat peanut. After a positive DBPCFC, dietary advice remained to avoid peanut. Children with severe reactions during DBPCFC (stridor, bronchoconstriction, and tachycardia) were advised to use a specified list of foods to achieve strict avoidance. This list indexes all food products and brands that definitely do not contain traces of peanut (provided by the Netherlands Nutrition Center, The Hague, The Netherlands). Food products are only listed when they are produced in peanut-free factories and use noncontaminated raw materials. Each year this list is updated with information provided by collaborating factories. All parents from children with a positive DBPCFC were informed that not-listed food products, and especially food products with "may contain peanut" labels, carry a certain risk of containing substantial amounts of peanut. All parents were asked to carefully document the ingestion of food products and describe any allergic reaction in a diary. This diary was compiled with help of a specialized dietician. After 3, 6, and 12 months, the parents of children were contacted, and dietary management and allergic reactions were evaluated with help of interviews and the diary.

TABLE I. Characteristics of study group (n = 27)

Characteristic	Number of children (%)
Sex	
Male	18 (67%)
Female	9 (33%)
Mean age	7.2 y
Atopic history	
Other food allergies	24 (89%)
Atopic dermatitis	18 (67%)
Allergic asthma	15 (56%)
Seasonal rhinoconjunctivitis	11 (41%)
Sensitization (elevated specific IgE)	
Peanut	23 (85%)
House dust mite	21 (78%)
Grass pollen	19 (70%)
Hen's egg	18 (67%)
Birch pollen	17 (63%)
Soy	15 (56%)
Cow's milk	10 (37%)
Previous reactions to peanut	
At least 1	17 (63%)
None	10 (37%)

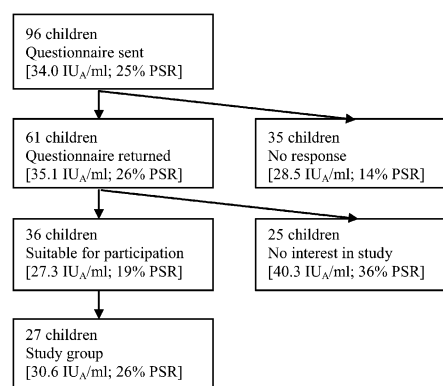
Statistics

Values were reported as the mean unless otherwise indicated. SPT, specific IgE, and ED were not normally divided, even after logarithmic transformation; hence, all calculations were performed with nonparametric tests. The relevance of placebo reactions was evaluated by using an adaptation of the Briggs model²³ by categorizing the data in nonresponders (n = 5), active responders (n = 19), placebo responders (n = 0), and combined placebo and active responders (n = 3). The Mann-Whitney *U* test was used to calculate differences in SPT, specific IgE, and ED between groups. The χ^2 test with Fisher correction was performed between the proportions of previous reactions between negative and positive DBPCFC. The Wilcoxon test was used to calculate paired differences in ED between subjective and objective symptoms. The Spearman ρ was calculated as a correlation factor between eliciting doses, severity of reaction, SPT, and specific IgE outcomes. Differences were considered significant if the *P* value was $\leq .05$. Statistical analysis was performed by using the statistical program SPSS (version 12.0; SPSS Inc, Chicago, Ill).

RESULTS

Patient characteristics

A group of 27 children (18 boys and 9 girls) participated in this study for complete evaluation of peanut allergy (Table I). The average age was 7.2 years (range, 3.7-15 years). To investigate whether this study group (n = 27) was a representative selection of the original peanut-sensitized population (n = 96), peanut-specific IgE levels and the percentages of previous severe reactions to peanut (dyspnea, bronchoconstriction, shock) were compared (Fig 1). Compared with the original population of peanut-sensitized children (n = 96), the study group had comparable specific IgE levels (30.6 vs 34.0 IU_A/mL), and the percentage of previous severe reactions to peanut was similar (26% vs 25%). The study group had lower specific IgE

**FIG 1.** Flow chart of patient selection, with specific IgE to peanut and the percentage of previous severe reactions to peanut (PSR) for each group.

levels (30.6 vs 40.3 IU_A/mL) and a lower percentage of previous severe reactions to peanut, dyspnea, bronchoconstriction, and/or shock (26% vs 36%) than the children who were not interested (n = 25). These differences were not statistically significant.

In the study group, other food allergies were present in 89%, atopic dermatitis in 67%, allergic asthma in 56%, and seasonal rhinoconjunctivitis in 41% of the children. Before the DBPCFC procedure, SPT and specific IgE levels were re-evaluated (Table II). SPT results varied from 0 to 23.9 mm² peanut/mm² histamine (mean, 6.9). IgE levels ranged from <0.35 IU_A/mL to >100 IU_A/mL (mean, 36.9 IU_A/mL). At this point, 1 child lost the sensitization to peanut. The majority of patients was also sensitized to common food and inhalant allergens. Seventeen children (63%) reported a previous allergic reaction to peanut during the peanut elimination period (a half to 10 years before the DBPCFC). In this group, 4 of 17 children had a reaction after skin contact, resulting in contact urticaria, associated with facial swelling in 2 children. Thirteen children (13/17) developed symptoms after ingestion: OAS (n = 11), urticaria, facial swelling and/or rhinoconjunctivitis (n = 12), abdominal pain, vomiting and/or diarrhea (n = 5), and dyspnea and/or bronchoconstriction (n = 7). One child had to be admitted to the hospital for severe dyspnea. These allergic reactions to peanut usually occurred after the inadvertent ingestion of peanut, peanut butter, peanut sauce, or pastries clearly containing peanut. Four children had eaten food products containing hidden peanut: a vegetarian meatball, chocolate ice cream, a chocolate candy bar, or a chocolate lollypop.

Factors related to positive DBPCFC

Double-blind placebo-controlled food challenge was positive in 81% of the children (22/27), confirming the diagnosis of peanut allergy. A positive DBPCFC was associated with previous reactions to peanut by history. Of the children without a previous reaction by history, 60% (6/10) had a positive DBPCFC, whereas 94% (16/17) of the children with a previous reaction had a positive DBPCFC (*P* = .047). In comparison, 73% of children

TABLE II. Sensitization, symptoms by history, and the results of DBPCFC for children without (n = 10) and with previous reactions to peanut (n = 17)

No.	Sensitization		History	DBPCFC			
	SPT*	IgE†		Symptoms‡	NOAEL§	ED subjective§	ED objective§
1	0	0	No previous reaction	None	—	—	—
2	1	0	No previous reaction	None	—	—	—
3	1	0	No previous reaction	None	—	—	—
4	2	0	No previous reaction	None	—	—	—
5	26	1.0	No previous reaction	Oas, fs, ap	300	1000	>3000
6	7	6.9	No previous reaction	Rc, vom	1000	—	3000
7	21	48	No previous reaction	Gu, rc, vom	1000	—	3000
8	1	7.5	No previous reaction	Oas, fs, rc, ap, dysp	300	1000	3000
9	8	4	No previous reaction	Oas, rc, ap, dia, dysp	1000	3000	>3000
10	10	100	No previous reaction	Rc, vom, bro	300	—	1000
11	0.2	55	Cu	None	—	—	—
12	1	0.42	Oas, fs, dysp	Oas	3000	>3000	—
13	3	35	Oas, urt, fs, rc	Oas, cu, fs	1000	3000	>3000
14	3	100	Oas, fs, vom, dysp	Oas, ap	1	10	—
15	3	3.0	Oas, vom, dysp	Oas, rc, ap	3000	>3000	>3000
16	9	3.3	Oas, fs, rc, vom, dysp	Oas, fs, urt, rc, ap	10	100	>3000
17	6	100	Cu, fs	Oas, vom	1	10	300
18	3	3.3	Oas, urt, vom	Nau, vom	300	1000	>3000
19	2	15	Cu	Oas, ap, vom	300	1000	3000
20	1	36	Oas, fs, bro	Oas, rc, vom	1000	3000	3000
21	6	21	Oas, urt	Oas, rc, ap, vom	100	300	1000
22	4	61	Oas, fs, rc, dia, bro	Oas, ap, vom, dia	100	300	>1000
23	10	93	Gu, fs	Gu, rc, ap, vom, dia	3000	>3000	>3000
24	13	2.5	Urt, rc	Oas, vom, rc, dysp	100	300	>300
25	10	100	Cu, fs	Rc, dysp	10	—	100
26	24	100	Oas, gu, fs	Gu, vom, str	300	—	1000
27	10	99	Oas, fs, rc, bro	Oas, gu, rc, bro, tach	300	1000	3000

*SPT in area peanut/area histamine.

†IgE in IU_A/mL (100, >100 IU_A/mL; 0, <0.35 IU_A/mL).

‡Symptoms: *oas*, oral allergy syndrome; *cu*, contact urticaria; *urt*, urticaria; *gu*, generalized urticaria; *fs*, facial swelling; *c*, conjunctivitis; *rc*, rhinoconjunctivitis; *ap*, abdominal pain; *vom*, vomiting; *dia*, diarrhea; *dysp*, dyspnea; *str*, stridor; *bro*, bronchoconstriction; *tach*, tachycardia.

§NOAEL and ED in mg.

with a positive DBPCFC had a previous reaction to peanut, compared with 20% of children with a negative DBPCFC. In our study, sensitization to peanut in children with a positive DBPCFC was significantly higher than in children with a negative DBPCFC, determined both by SPT ($P = .002$) and by specific IgE ($P = .010$). Cut-off levels for SPT wheals or specific IgE could not be calculated because the number of patients with a negative DBPCFC was too small ($n = 5$).

Symptoms during DBPCFC

Symptoms during DBPCFC varied in severity from mild (OAS, several urticaria, abdominal pain) to severe (bronchoconstriction, tachycardia). Table II describes the reactions during DBPCFC, as well as previous reactions and sensitization for each patient, displayed in order of severity of symptoms during DBPCFC. Usually, symptoms developed within 30 minutes after ingestion. Generalized urticaria developed later in the course of an allergic reaction, usually 50 to 90 minutes after the last ingested dose.

Late reactions like deterioration of atopic dermatitis were not observed in this study. Severe reactions during

DBPCFC involving the respiratory tract and/or the circulatory system were seen in 3 of 22 (14%) children, but only at high dose. The first child developed vomiting and rhinoconjunctivitis, followed by severe bronchoconstriction after ingestion of 1 g peanut flour. The second child vomited after 1 g, started coughing after an hour, and subsequently developed stridor and generalized urticaria. The third child complained of OAS after the ingestion of 3 g peanut flour, immediately followed by acute dyspnea caused by bronchoconstriction. Systemic administration of antihistamines and adrenaline, and inhalation of steroids and bronchodilators, led to a temporary improvement. After 15 minutes, generalized urticaria, severe dyspnea, and tachycardia developed, needing a second treatment course. Another 2 children with symptoms like vomiting and rhinoconjunctivitis developed generalized urticaria that worsened despite intravenous antihistamines and steroids, but responded well after additional administration of adrenaline. Overall, 20 of 22 children developed objective symptoms during DBPCFC, whereas 2 of 22 exclusively reported subjective symptoms. Subjective symptoms were reported after 7% (5/74) of the placebo portions by 3 children. Subsequently, all 3 patients

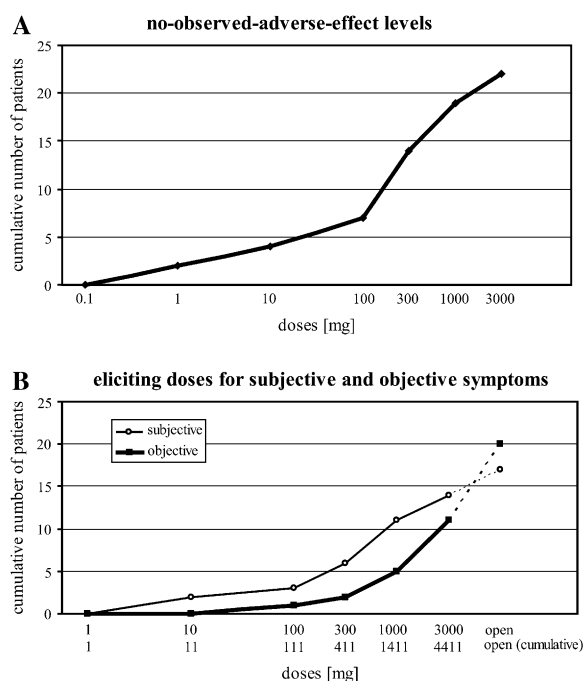


FIG 2. A, Distribution of NOAEL. B, Distribution of ED for subjective and objective symptoms.

developed objective reactions to active portions. Placebo reactions had no effect on the final results using an adaptation of the Briggs²³ model. Determination of the NOAEL was also not influenced by the placebo reactions.

To determine whether the severity of the reaction during DBPCFC was related to sensitization, symptoms were graded according to the scale of Mueller²² from 0 to 4. The severity of the reaction during DBPCFC was weakly correlated to SPT reactivity ($p = 0.49$; $P = .021$), but not to specific IgE levels or to the severity of the reaction by history.

NOAEL and ED for subjective and objective symptoms as determined by DBPCFC

All children tolerated a dose of 1 mg peanut flour. Hence, the NOAEL in our study was 1 mg peanut flour, which corresponds to 2 mg peanut (Fig 2, A). The lowest ED was 10 mg ($n = 2$), causing OAS. The ED for subjective symptoms ranged from 10 mg to 3 g and was significantly lower than that for objective symptoms that ranged from 100 mg to 3 g ($P = .002$; Fig 2, B). Subjective symptoms were OAS, nausea, and/or abdominal pain. Objective symptoms consisted of several urticaria, generalized urticaria, facial swelling, rhinoconjunctivitis, vomiting, diarrhea, hoarseness, stridor, bronchoconstriction, and/or tachycardia. In 2 of 22 reacting children, no objective signs were observed. Five (5/22) children developed objective symptoms without subjective symptoms. In 12 of 22 cases, subjective symptoms preceded objective symptoms. In these children, ED for subjective symptoms

TABLE III. Accidental allergic reactions during a 12-month follow-up period in 3 different dietary management groups

Accidental allergic reactions	Dietary management		
	No restriction (n = 5)	Less strict (n = 11)	Strict (n = 11)
To "may contain peanut" products	0	3	0
To other products containing peanut	0	3	0
Number of patients	0	4	0

were ≥ 10 mg, and for objective symptoms ≥ 300 mg. In 3 of 22 children, ED for subjective and objective reactions were similar (≥ 3 g). In children without a previous reaction to peanut, the ED was ≥ 1000 mg, and in the group with previous reactions ≥ 10 mg. Children with previous reactions (by history) to hidden traces of peanut ($n = 4$) had a low ED of 10 mg, 100 mg, and 300 mg ($n = 2$).

With respect to SPT or specific IgE levels, a correlation with ED was not present. The severity of the reaction by history or during DBPCFC, as graded by Mueller,²² was not correlated to the ED either.

Dietary management during a 12-month follow-up period

Dietary restrictions for peanut were no longer necessary for the 5 children with a negative DBPCFC (Table III), and they began the introduction of peanut into their diet. Twenty-two children had a positive DBPCFC. After DBPCFC, 11 children (11/22) had very strict dietary management achieved by using a specified list indexing all food products and brands that did not contain traces of peanut. The other group (11/22) had a less strict peanut free diet and did not use the specified list. The parents of 10 children (10/11) indicated that they occasionally used food products that might contain traces of peanut.

All 3 groups were followed for 12 months. During the 12-month follow-up period, all of the children with negative DBPCFC ingested peanuts without problem. The children that followed the strict diet using specified lists of peanut-free products did not have any allergic reaction to peanut. In the group that was less strict, mild OAS was reported by 3 children after the ingestion of foods with a "may contain peanut" label. Because of accidental ingestion, 3 children from this same group had a mild to moderate allergic reaction. Two children developed a reaction consisting of vomiting (associated with facial swelling in 1 child) after the ingestion of crisps from a bowl that contained peanuts before. The third child developed hoarseness and stridor 1 hour after the ingestion of ice cream with peanut and chocolate crunch topping.

DISCUSSION

The aim of this study was to determine the NOAEL and the ED for peanut in a representative group of peanut-

sensitized children and to relate these data to history and sensitization to peanut. Furthermore, we aimed to evaluate the outcome of dietary management during a 12-month follow-up period.

In our opinion, this is the first study that has determined a NOAEL in peanut-sensitized children. We used the recently published consensus protocol developed to determine a NOAEL and lowest ED. Most studies in children so far reported reactions to the first dose, rendering the study inappropriate to determine a NOAEL.²⁴⁻²⁶ In our study, the NOAEL was 1 mg peanut flour, corresponding to 2 mg peanut. This is within the limits of currently available detection systems of peanut (0.2-1.2 mg/kg).²⁷ The international consensus protocol was developed to set uniform guidelines about performing DBPCFCs. In this way, results of our study can be combined with other studies on this subject. It might be good to challenge larger numbers of patients, preferably in other centers and countries, to increase the value of the obtained data.

A major concern in most studies is that patient selection occurred on the basis of previous reactions and sensitization, and the most sensitive patients were excluded.²⁴⁻²⁶ One of our objectives was to study a representative group of peanut-sensitized children. The children in our study had comparable specific IgE levels and incidence of previous severe reactions as the initially contacted peanut-sensitized population (Fig 1). During DBPCFC, 14% had a severe reaction. One child (4.5%) developed cardiovascular symptoms, which is comparable with the study of Morisset et al²⁴ (3%). Together, these data might reflect the fact that we did not exclude the more sensitive patients and studied a representative group of children.

The lowest ED in our study group was 10 mg, resulting in subjective symptoms (OAS) and corresponding to 20 mg peanut. This is in line with data from another study determining ED for peanut in children who found a lowest ED of 5 mg.²⁴ In adults, EDs as low as 400 µg whole peanut have been reported, which is 50-fold lower than in our study.¹⁰ Because at these low doses only OAS was reported, adults might be more aware of these particular symptoms. Usually adults have more concomitant food allergies, especially pollen-related, that commonly cause OAS.²⁸ This also explains why in children more objective symptoms (91%) were reported than in adults.^{9,11} The ED for objective symptoms was significantly higher, 100 mg, corresponding to 200 mg whole peanut. This is comparable with data found in adults by Wensing et al¹¹ (40 mg) and Hourihane et al⁹ (20 mg whole peanut).

Factors that may influence the ED are sensitization, the severity of the peanut allergy,¹¹ and the matrix in which the peanut is hidden.²⁹ In our study, the ED was not correlated to the level of peanut-specific IgE, SPT reactivity, or the severity of peanut allergy by history. Wensing et al¹¹ showed that in adults, low ED during challenge was correlated to severity of previous reactions, and to a lesser extent to reactions during DBPCFC. This result could not be reproduced in children. The ED in children with previous reactions to hidden peanut were all in the low range (10-300 mg peanut flour), suggesting that the ED

reflects the situation in daily life. The ED, together with other factors as sensitization and history, might be used to come to a tailor-made dietary advice. We suggest only a less strict diet to patients with a history of exclusively mild reactions, a high ED (if measured), and no history of reactions to traces (checked by a trained dietitian).

Dietary management on the occurrence of allergic symptoms in everyday life was also studied. So far, data in literature are almost nonexistent.^{30,31} We are aware of the unique situation in The Netherlands that allows us to use a list that indexes products "free from peanut." In addition, all patients received information on how to avoid peanut in daily life, with special attention to foods being likely unsafe. The effect of such a strict regimen on the occurrence of accidental allergic reactions appeared beneficial, because no children that carefully followed the advice had a reaction during the 12-months follow-up period. However, 10 of 27 children, including 1 child with a moderate to severe reaction (generalized urticaria with complete loss of bowel control) during DBPCFC, admitted to be less strict with dietary management than advised. This finding regarding compliance with respect to medical advice in patients with chronic atopic diseases has been reported earlier.^{32,33} Remarkably, 3 of the 6 reactions reported during follow-up could be related to "may contain peanut"-labeled products. This is especially important with regard to the increasing use of "may contain peanut" labeling¹⁶ because of recent regulatory changes,¹⁴ which have a great effect on the food choices of allergic individuals and may influence the compliance to a diet in a negative way. The fact that a substantial number of patients in daily practice already follows a less strict diet underlines the importance of good instructions of patients regarding the safety of foods with special attention to foods labeled as "may contain peanut." Data on NOAEL will contribute to future guidelines regarding the development of safe foods.

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