

How much is too much?: Threshold dose distributions for 5 food allergens

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Background: Precautionary labeling is used to warn consumers of the presence of unintended allergens, but the lack of agreed allergen thresholds can result in confusion and risk taking by patients with food allergy. The lack of data on threshold doses below which subjects are unlikely to react is preventing the development of evidence-based allergen management strategies that are understood by clinician and patient alike.

Objective: We sought to define threshold dose distributions for 5 major allergenic foods in the European population.

Methods: Patients with food allergy were drawn from the EuroPrevall birth cohort, community surveys, and outpatient clinic studies and invited to undergo a food challenge. Low-dose, double-blind, placebo-controlled food challenges were undertaken with commercially available food ingredients (peanut, hazelnut, celery, fish, and shrimp) blinded into common matrices. Dose distributions were modeled by using

interval-censoring survival analysis with 3 parametric approaches.

Results: Of the 5 foods used for challenge, 4 produced similar dose distributions, with estimated doses eliciting reactions in 10% of the allergic population (ED₁₀), ranging from 1.6 to 10.1 mg of protein for hazelnut, peanut, and celery with overlapping 95% CIs. ED₁₀ values for fish were somewhat higher (27.3 mg of protein), although the CIs were wide and overlapping between fish and plant foods. Shrimp provided radically different dose distributions, with an ED₁₀ value of 2.5 g of protein.

Conclusion: This evidence base will contribute to the development of reference doses and action levels for allergens in foods below which only the most sensitive subjects might react. (J Allergy Clin Immunol 2014;■■■■:■■■■-■■■■.)

Key words: Food, allergy, threshold, peanut, hazelnut, celeriac, fish, shrimp, EuroPrevall

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The prevalence of allergic disease, including IgE-mediated food allergy, has increased in recent decades, and it is now estimated to affect up to 5% to 7% of infants and 1% to 2% of adults. Food allergies in infancy are dominated by cow's milk and hen's egg but are largely outgrown by school age.¹ However, allergy to peanut persists into adulthood, and is the dominant allergy in the United Kingdom,² France,³ North America,⁴ and Australia.⁵ In adulthood patterns of food allergies change, with new allergies emerging to foods such as crustacean and molluscan shellfish and fresh plant foods associated with sensitization to pollen. The lack of a definitive cure means patients with food allergy have to practice lifelong stringent avoidance of the foods to which they react. Furthermore, those at risk of severe reactions must carry rescue medication in case of accidental consumption of their problem food. Despite such management strategies, accidental ingestion of offending foods remains a major cause of severe allergic reactions,⁶ with manufactured and restaurant foods being largely responsible for causing fatal reactions.⁷ Food avoidance also imposes a significant burden on allergic consumers and their families and communities, impairing quality of life.⁸ Legislation is in place around the world that requires allergenic ingredients to be declared when used in prepackaged foods, irrespective of their level of inclusion.⁹ However, managing food allergens to avoid their presence in products in which they are not part of a recipe remains an issue. This can be challenging because exposure to tiny amounts of allergenic ingredients can trigger a reaction in some subjects, with a kiss from someone who has been eating a problem food being sufficient to trigger a reaction.¹⁰

Precautionary labeling to warn allergic consumers of the risk posed by such cross-contact allergens has become widespread. However, such warnings have increasingly lost their effectiveness because they are applied in an inconsistent manner and are not always reflective of either the likelihood of allergen

Abbreviations used

DBPCFC: Double-blind, placebo-controlled food challenge
ED₁₀: Estimated dose eliciting a reaction in 10% of a study population
OAS: Oral allergy syndrome

contamination¹¹ or a clinical reaction. As a result, consumers with food allergy are confused about ingredients contained in commercial food products.¹² They consider information to be unclear or insufficient, leading to personal stress and feelings of insecurity¹³ and potential risk taking. In addition, there is confusion about interpretation of precautionary labels among health professionals who provide allergic consumers with advice on how to manage their condition.

Data are required as to what levels of allergen contamination can be considered to pose a small risk for most consumers with food allergy to develop more meaningful allergen labeling and management strategies. Regulatory authorities and others have taken the view that although threshold doses for allergens exist below which reactions do not occur, such thresholds have yet to be defined.^{14,15} Such information has been gained from human subjects with food allergies by using low-dose oral food challenges to define the question of "how much is too much."¹⁶ A wealth of data have been collected for peanut, which has allowed modeling of dose distribution, an approach that is now well accepted,^{15,17-20} forming a sound basis for assessing the risk posed by small amounts of this most notorious allergenic food.²¹ A major aim of the EuroPrevall project²² was to gather threshold data in the European population through studies undertaken in a pan-European birth cohort²³ together with community and related outpatient clinic studies.²⁴ Food allergy

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was confirmed in EuroPrevall by using the gold standard diagnostic approach of the double-blind, placebo-controlled food challenge (DBPCFC).²⁵ This article describes dose distribution models based on EuroPrevall DBPCFC data for 5 major allergenic foods (peanut, hazelnut, celeriac, fish, and shrimp) and their use to estimate the estimated dose likely to elicit reactions in 10% of a study population (ED₁₀; ie, the European population with food allergy). Such evidence will support the development of reference doses and action levels for allergens in foods in the future and thereby aid food allergy and allergen management, improving safety for consumers with food allergy.

METHODS

Participant populations and characteristics

The population of patients with food allergy who underwent DBPCFCs (see Table E1 in this article's Online Repository at www.jacionline.org) came from the EuroPrevall birth cohort (study A),²³ and those having probable food allergies came from the EuroPrevall community surveys in adults and school-age children (study B) and an outpatient clinic population (study C).²⁴ Food-specific IgE levels were determined by using ImmunoCAP (Thermo Fisher Scientific, Uppsala, Sweden) with a range of foods and inhalant allergens in serum samples from the cohorts, with strategies appropriate to the age group and study, as previously described.^{23,24,26} Participants underwent threshold challenges as follows. Patients in study A were selected if they had either a positive case history of a potential allergic reaction to one of the 5 foods under investigation or were sensitized to one of the 5 foods (increase food-specific serum IgE level >0.35 KU/L) or had a positive skin prick test response (≥ 3 mm) without clear clinical tolerance to the sensitized food. Patients in study B were selected if they had a positive case history of an allergic reaction to one of the 5 foods under investigation and a corresponding increase in specific IgE levels (>0.35 KU/L) to the same food. Patients in study C were selected solely on the criterion of a positive case history to one of the 5 foods. Patients with a clear-cut case history of an anaphylactic reaction according to the methods of Cochrane et al²⁵ and Sampson et al²⁷ have been excluded from challenge. Detailed descriptions of the populations, IgE measurements, and exclusion criteria are presented in Supplement E1 and Table E1 in this article's Online Repository at www.jacionline.org.

DBPCFCs

DBPCFCs were undertaken by using a common harmonized protocol, which consisted of participants ingesting increasing doses of food matrix (either alone [placebo challenge] or containing allergen [active challenge]) until they had an objective (externally observable) reaction or reported persistent and/or severe subjective reactions. Challenges were performed in a harmonized manner by using allergenic ingredients and matrices appropriate for the age group undergoing challenge, with increasing doses delivered at intervals of 20 minutes starting with 3 μ g of protein up to a cumulative dose of 1 to 6 g of protein depending on the food (see Tables E2 and E3 in this article's Online Repository at www.jacionline.org). The 2 challenges were performed in a randomized manner 1 week apart. Twenty symptoms were monitored and classified as either objective or subjective (see Table E4 in this article's Online Repository at www.jacionline.org). Challenges were stopped on occurrence of either objective symptoms or persistent (45 minutes) and severe subjective symptoms. Stop criteria were as described by Bindslev-Jensen et al.²⁸

Data analysis

Clinical records were extracted and collated from the EuroPrevall database. Participants with some form of immediate hypersensitivity reaction (subjective or objective) to an active but not a placebo dose were included in the reactive reference population used for analysis. Reactions had to occur 2 or less hours after the last dose. Certain patients responded only with a

delayed-type reaction (eg, exacerbation of atopic eczema) and, although considered reactors, were not included in the reference population because they could not be classified as having an immediate hypersensitivity reaction. Participants were classified as tolerant if they showed no reaction during the DBPCFC, whereas placebo reactors experienced either subjective or objective symptoms to one of the placebo doses at 2 hours or less after the last dose.

Symptoms were ranked in order of severity, as determined by a consensus meeting of the EuroPrevall clinical partners and visualized for the "reactive reference" population as a function of dose. Dose distributions were modeled for each food type, and from this, estimates of ED₁₀ values (doses at which an allergic reaction would be elicited in 10% of the population) were calculated. These models were built by using interval-censoring survival analysis.²⁰ The interval-censoring approach was carried out by using the survival package²⁹ in R³⁰; left- and right-censored data are presented in Table E2. ED₁₀ values were calculated by using parametric models based on either log-normal, log-logistic, or Weibull distributions. CIs for the ED₁₀ values were calculated by taking the 2.5th and 97.5th percentiles of the bootstrap distribution of ED₁₀ values generated by using 10,000 bootstrap samples.

RESULTS

Challenged populations

Analysis of challenge data for 5 foods (hazelnut, peanut, celeriac, fish, and shrimp) has been undertaken, drawing on participants from the pan-European EuroPrevall studies (Fig 1 and see Supplement E1). Of 436 challenged patients, we included as our reactive reference population 244 subjects with a median age of 24.2 years. Because of the patterns, prevalence, and inherent age distribution of the cohort with food allergy, challenges for hazelnut, celeriac, and shrimp were undertaken largely in adults (median age, 30.8–32.2 years) and younger subjects for peanut and fish (10.4 and 14.2 years, respectively). Although some participants challenged to foods, such as peanut, were drawn from many centers, others, such as celeriac, fish, and shrimp, were limited largely to the Swiss and Icelandic populations, respectively (Fig 1). The reactive peanut population comprised approximately 56% of the participants from the older population (median age 29.6 years), with the birth cohort contributing approximately 44% of the participants (median age 1.9 years). In general, 54% to 69% of the challenged population were classified as reactive, with rates of placebo reactions ranging from 6% to 13%. Peanut produced lower rates of reaction, with only 44% of the total challenged population classified as reactive. This was surprising because rates of reaction to hazelnut, an allergenic plant food with a similar allergen profile, were higher (69%).

Of the subjects for whom serum IgE measurements were available, all those included in the challenge population were sensitized to the food with which they were challenged. However, there were no differences in food-specific IgE levels between the reactive and tolerant subjects, and levels were notably low in the shrimp challenge population (Fig 2 and see Table E3). The hazelnut and peanut challenge populations were also frequently sensitized to birch pollen and house dust mite, and although the celery challenge population was more highly sensitized to birch, they showed little reactivity to house dust mite compared with the other participants included.

Symptoms and eliciting doses

Initially, symptoms provoked by the different allergenic foods during DBPCFCs were mapped as a function of dose by using a ranking of symptoms based on a previously developed classification (Fig 3).³¹ Itching of the oral mucosa, a symptom

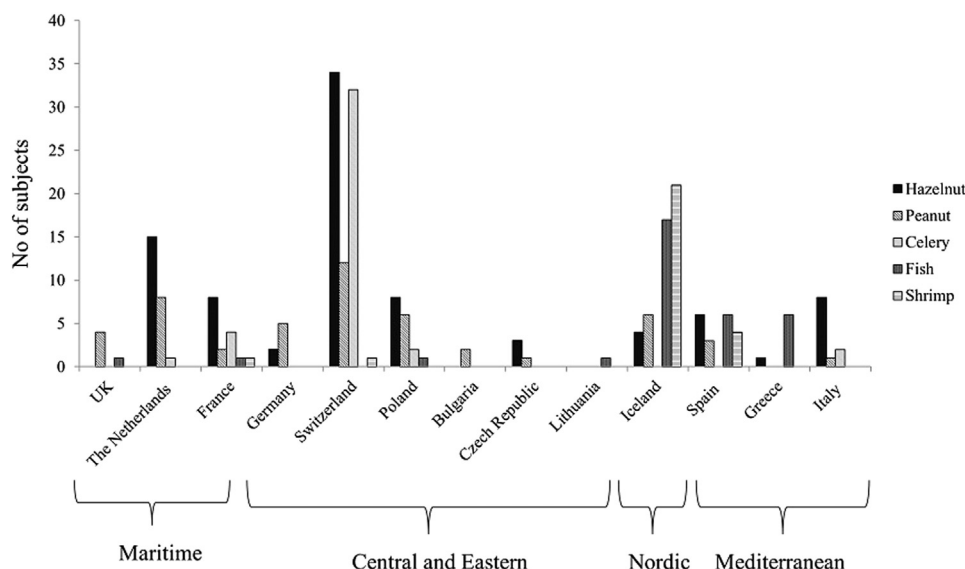


FIG 1. Geographic distribution of the reactive patients used for dose distribution modeling by food.

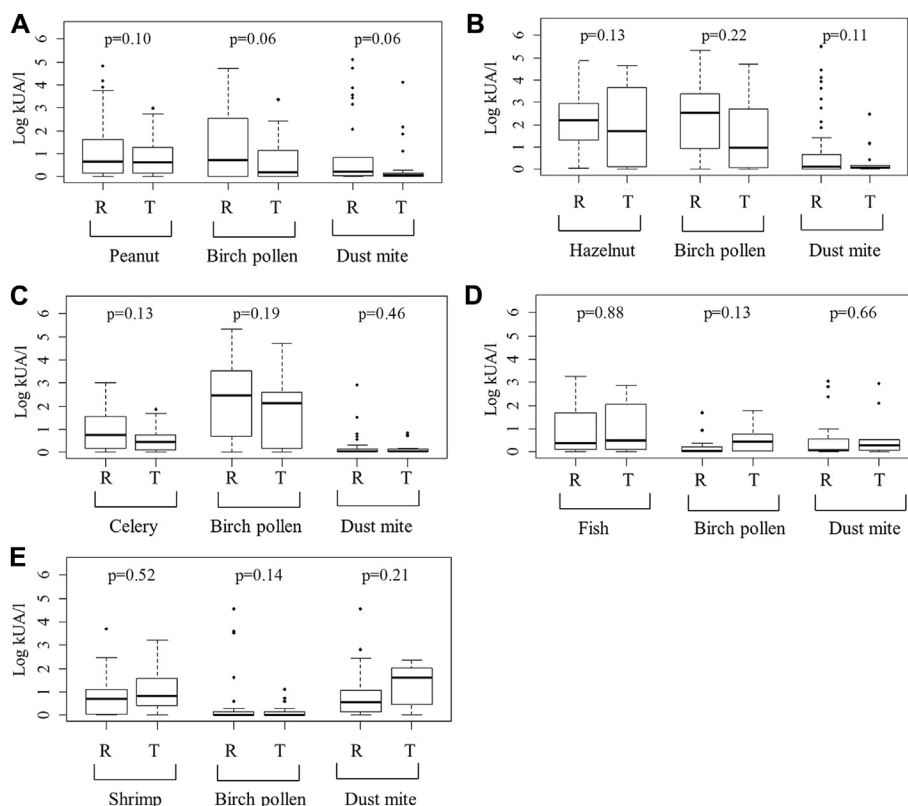


FIG 2. Comparison of food and inhalant allergen-specific IgE levels in reactive and tolerant subjects: **A**, peanut; **B**, hazelnut; **C**, celery; **D**, fish; and **E**, shrimp. Box and whisker plots represent medians and 25th and 75th percentiles as the box and 2.5th and 97.5th percentiles as the whiskers. *P* values represent tests comparing specific IgE levels between reactive and tolerant subjects. *R*, Reactive population; *T*, tolerant population.

known as oral allergy syndrome (OAS), was systematically recorded only in older participants. Several patients reacted at the first dose (3 μ g of protein) with subjective symptoms, despite this dose having been designed as a likely “no-effect” level. This was observed with all the foods. Many of the patients

experiencing subjective symptoms initially had objective symptoms after consuming a higher allergen dose. A different pattern of reactivity was observed for shrimp, with less than 10% of participants experiencing OAS for doses 1 to 5, which suddenly increased to greater than 20% from doses 6 to 9 when

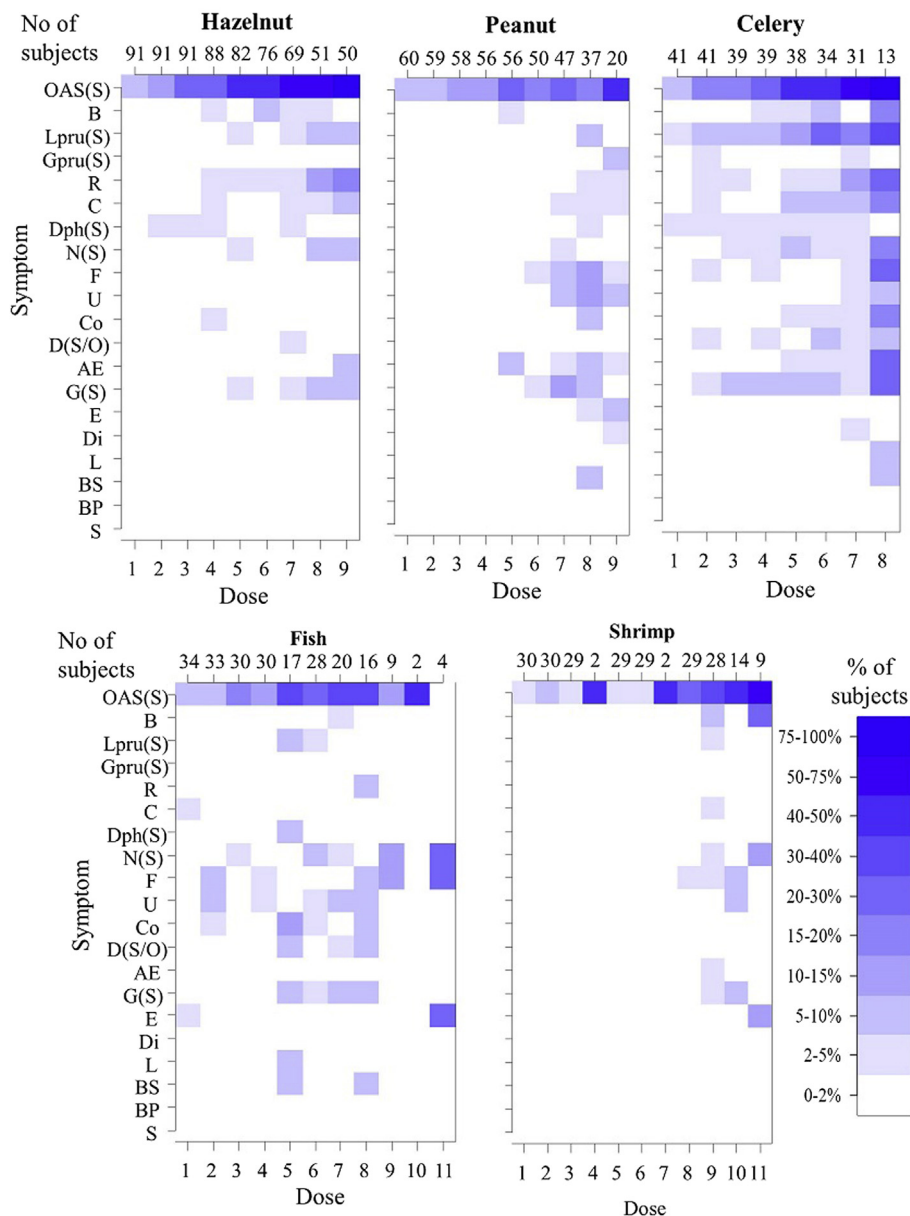


FIG 3. Symptom patterns to major allergenic foods observed during food challenges. The intensity of blue shading denotes the percentage of challenged participants responding with a given symptom. The number of subjects given a particular dose is indicated across the top of the plots. No dose 9 was given in celeriac challenges. Subjective symptoms are marked S and ranked as described in Table II and Supplement E1. AE, Angioedema; B, blister of the oral mucosa; BP, decrease in blood pressure; BS, bronchospasm; C, conjunctivitis; Co, cough; D, dyspnea; Di, diarrhea; Dph, dysphagia; E, emesis; F, flush; G, gastric pain and/or burning; Gpru, generalized pruritus; L, laryngeal edema; Lpru, localized pruritus; N, nausea; R, rhinitis; S, shock; U, urticaria.

more than 1 g of shrimp protein was given. Two subjects in the reactive reference population reacted with objective symptoms at the first dose (3 μ g of either peanut or fish protein), and 2 subjects had reactions between doses 1 and 2 (3–30 μ g of celeriac protein, Table I). However, the majority of participants had to consume much higher doses of most of the foods before experiencing objective rather than subjective symptoms. Dose distributions were modeled by using interval-censoring survival analysis for either subjective, objective, or both types of symptoms. Because symptoms were recorded at discrete dose

levels only, the exact dose level triggering a reaction is not known. For a participant reacting to the first dose, only the lowest observed adverse effect level is known, and the data are said to be left censored, with the response threshold lying between zero and 3 μ g of protein. Conversely, if a participant did not react during the challenge, only the no observed adverse effect level is known, and the data are right censored (threshold beyond the last dose). This feature of the data, known as interval censoring, has been fully accounted for in our modeling approach. Three different distributions, log-normal, log-logistic, and Weibull,

TABLE I. Case descriptions of lowest-dose responders experiencing objective symptoms

Food	Dose interval (mg protein)	Symptoms	Study	Center
Hazelnut	0.033-0.333 mg	OAS,* blisters of the oral mucosa	C	Switzerland
	0.033-0.333 mg	OAS,* dysphagia, dyspnea, angioedema, bronchospasm	C	The Netherlands
Peanut	0-0.003 mg	OAS,* flush, urticaria	A	United Kingdom
Celeriac	0.003-0.033 mg	OAS,* rhinitis, other (sneeze)	C	Switzerland
	0.003-0.033 mg	OAS,* localized pruritis, cough, flush, dyspnea	C	Switzerland
Fish	0-0.003 mg	Cough, emesis	A	Iceland
	0.333-3.333 mg	Flush	A	United Kingdom
	0.333-3.333 mg	Urticaria	C	Iceland
Shrimp	132-1132 mg	OAS* and flush	C	Iceland

*OAS was defined in this study as itching of the oral mucosa.

TABLE II. ED₁₀ values (in milligrams of protein) and 95% CIs for EuroPrevall DBPCFC-reactive participants determined by using an interval-censoring approach with log-normal parametric curve fitting, with all symptoms, only subjective symptoms, or only objective symptoms recorded

Food	Symptom type		
	All	Subjective	Objective
Hazelnut	0.01 (0.002-0.05)	0.009 (0.002-0.05)	8.5 (2.3-37.6)
Peanut	0.03 (0.002-0.37)	0.007 (0.0002-0.17)	2.8 (0.2-36)
Celeriac	0.002 (0.0002-0.03)	0.002 (0.0001-0.03)	1.6 (0.2-19.6)
Fish	0.2 (0.01-4.8)	0.2 (0.005-8.2)	27.3 (5.3-171.2)
Shrimp	10.4 (0.1-1032)	9.3 (0.1-933)	2504 (1152-5909)

Symptoms are described in Table E4.

were used but produced essentially similar results (Table II); hence data are only presented for log-normal values in Fig 4. The subjective symptom curves (see Figs E1-E5 in this article's Online Repository at www.jacionline.org for other foods) are shifted to lower doses compared with the objective symptom curves, with curves modeled for all symptoms resembling those based on subjective symptoms. This is because response intervals are based on the first response and hence influenced more strongly by subjective symptoms when all symptoms are considered. These curves produced estimated doses of hazelnut protein likely to elicit a reaction in 10% of the allergic population of 10 µg for subjective symptoms and 9 mg for objective symptoms (Fig 4, A, and Table II). For hazelnut, 45% of the challenged population had objective symptoms during the challenge, with the remaining challenges being right censored, where subjects reacted with persistent subjective symptoms. Although these represent a large set of low-dose challenge data, they are relatively small in terms of the variability observed in human studies. The relatively large CIs with ED₁₀ values of 8.5 to 10.1 mg and 95% CIs of 2.1 to 51.0 mg estimated by using the different distributions reflect the fact that each dose interval is populated by relatively few data points. Because hazelnut had a larger reactive population, ED₁ and ED₅ values based on objective symptoms were calculated for a log-normal distribution as being 0.055 mg (95% CI, 0.007-0.560) and 1.5 mg (95% CI, 0.3-8.4), respectively.

The peanut data set shows similar behavior to hazelnut (Fig 4, A and B), with very low ED₁₀ values for subjective symptoms and predicted ED₁₀ values of 2.8 to 6.6 mg of protein for objective symptoms (95% CI, 0.5-51.7 mg; Table II). However, the celeriac-reactive population had symptoms at lower doses compared with the peanut- and hazelnut-reactive population,

with objective symptom ED₁₀ values of 1.6 to 2.8 mg of protein (95% CI, 0.2-30 mg; Fig 4, C). A greater proportion of celeriac-reactive participants (63%) reacted with objective rather than subjective symptoms, such as OAS. Dose distribution models of the population with fish allergy had objective symptom ED₁₀ values greater than those of the population with plant-derived food allergy, ranging from 25.8 to 32.6 mg of protein (95% CI, 5.3-171.2 mg of protein; Fig 4, D). Shrimp, the other studied animal food allergen, showed a completely different pattern of reactivity than all the other foods studied. Much higher objective symptom ED₁₀ values were obtained than for any other food (approximately 2.5 g of protein; 95% CI, 1.1-5.9 g; Fig 4, E). Although the uncertainty on these estimates is larger because of the smaller number of observations (27 participants), these and the number of right-censored cases (>60% with no observed adverse effect levels for all but 1 participant between 4 and 9 g) indicate that subjects had to consume much greater amounts of shrimp to elicit objective responses during oral food challenge than any of the other foods.

DISCUSSION

The data from the EuroPrevall pan-European cohorts for peanut produced an ED₁₀ value for objective symptoms similar to those previously published by using the interval-censoring survival analysis approach in other populations with peanut allergy.²⁰ A log-normal dose distribution produced an ED₁₀ value of 2.8 mg of protein, which equates to 11.2 mg of peanut seed containing 25% protein (dry weight). It is of the same order as the ED₁₀ value of 12.3 mg of peanut seed defined among 450 participants used in the study by Taylor et al.²⁰ For the other foods, the ED₁₀ values equate to 9 mg of hazelnut protein (67 mg of hazelnut; 13.7% protein [dry weight]), 1.6 mg of celeriac powder (100 mg of raw celeriac root; 1.5% protein wet weight), 27 mg of fish (152 mg of raw cod fish flesh; 17.8% [wet weight]), and 2.5 g of shrimp (12.8 g of raw shrimp flesh; 20.3% [wet weight]). The wide CIs (typically covering 2 orders of magnitude) for the EuroPrevall dose distributions mean it is not statistically valid to differentiate between the ED₁₀ values calculated for the 3 plant-derived foods and fish, although the latter value was higher by a factor of 2. Comparison of these threshold doses with other published data³²⁻³⁴ suggests that although the ED₁₀ values for hazelnut are similar, the ED₁₀ values for roasted peanut are much higher (133.8 mg [95.9-186.6 mg]) in the Danish population. This difference might result from variations in the challenge protocol because Eller et al³² used a combination of open challenges (with 1 mg of peanut as the first

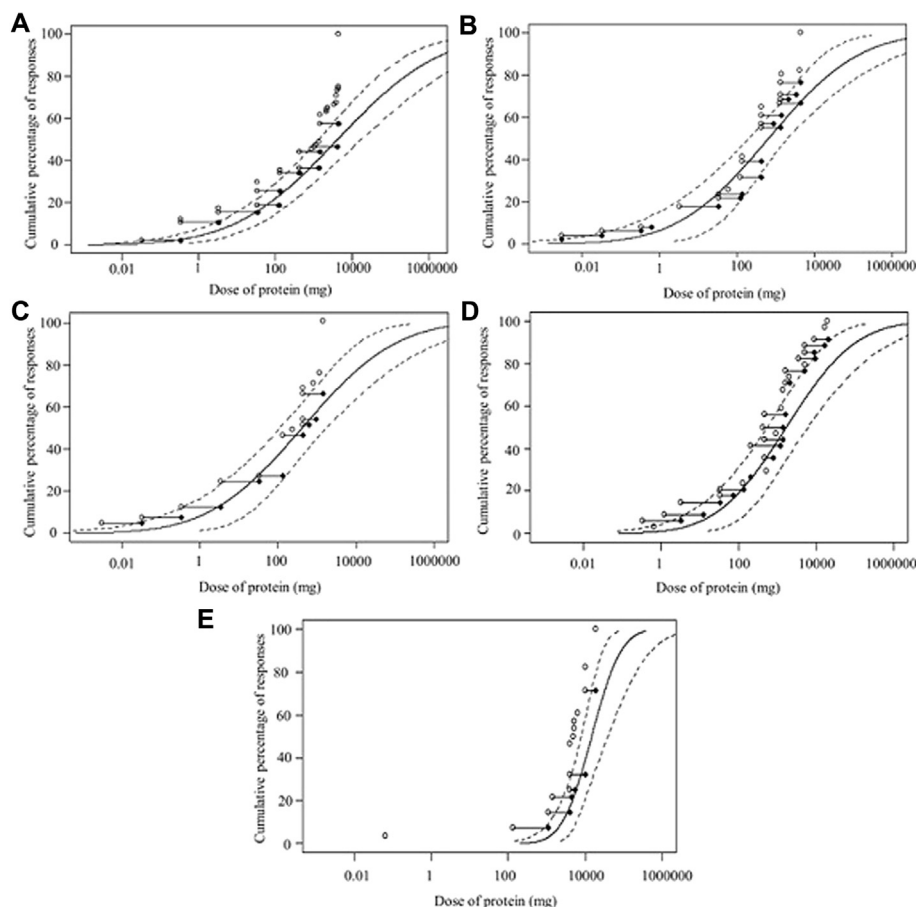


FIG 4. Dose distributions for objective symptoms to 5 foods: **A**, hazelnut; **B**, peanut; **C**, celery; **D**, fish; and **E**, shrimp. *Dashed lines*, 95% CI; *open circles*, no observed adverse effect level (NOAEL); *solid circles*, lowest observed adverse effect level (LOAEL); *open and solid circles connected by a solid line*, censored interval. Unlinked NOAELs or LOAELs represent either right- or left-censored observations.

dose) and DBPCFCs (with a first dose of 85 mg of peanut), whereas in the current study the first dose was 3 μ g of protein. Contrary to anecdotal evidence, shrimp behaved quite differently and produced a dose distribution for which the estimated ED₁₀ value was almost 100-fold greater than the other foods studied, although it was qualitatively similar to that published for soybean.³⁵ Anecdotes of patients reacting to traces of shrimp suggest patient sensitivity might be greater toward raw shrimp compared with the well-cooked shrimp protein used in the challenges. However, these data indicate that traces of cooked shrimp that might be found in manufactured food products pose much less of a risk to allergic subjects than the equivalent for foods such as peanut, hazelnut, celeriac, and fish.

In the total challenge population 2 participants responded with objective symptoms at the first dose (3 μ g of protein), indicating that some subjects' threshold doses are less than this level. Many more subjects reacted with subjective symptoms at this level, only having objective symptoms at higher doses. This observation supports the value of such subjective symptoms as a warning of the potential presence of allergen that should be heeded by patients with food allergy, although these symptoms do not necessarily occur before a systemic reaction. Threshold doses below which no patient with food allergy will react are a theoretic possibility but appear to be less than the 3- μ g protein level used in this study. Thus it is unlikely that threshold doses can be derived

and then implemented in food factories in a manner that protects all patients with food allergy against any reaction.

These data also support the view that ED₅ or ED₁ values might be more appropriate to use as a basis for deriving action levels because they will offer a greater level of protection to patients with food allergy. Determining such levels accurately will require larger dose distribution data sets for each food by using low-dose challenge protocols because the small numbers of subjects reacting at the 3- to 30- μ g level disproportionately skew the analysis of the data by widening the CIs. Additional data on dose distributions modeled by using data from immunotherapy trials might contribute to our knowledge regarding "how much is too much."

One of the unique values intrinsic to the EuroPrevall data sets is that they are set within the context of 2 population studies undertaken through a birth cohort and a community survey in adults and schoolchildren complemented by an outpatient clinic study, drawing on patients from across Europe. In this way, although not perfect, they are more representative of the European population as a whole than highly selected patient groups recruited for immunotherapy. As with all threshold studies, there are concerns that exclusion of patients at risk of severe reactions might bias results, a concern that can only be resolved by undertaking low-dose challenges in patients with a history of anaphylaxis.

The severity of the reaction and its relationship to dose also needs to be considered in defining reference doses as a basis for action levels for allergens. The EuroPrevall data indicate that celeriac seems to trigger more severe reactions at lower doses and elicits a different pattern of reactions than hazelnut, although both populations were sensitized to pollen. One explanation might be the type of cross-reacting allergens between pollen and plant food because celeriac allergy with severe symptoms is linked to mugwort pollen sensitization, whereas hazelnut allergy is related to birch pollen sensitization. Thus for a given dose of protein, hazelnut elicited symptoms, such as rhinitis, that are reminiscent of those observed to pollen, whereas celeriac elicited more severe reactions involving the respiratory system, skin, and gastrointestinal tract. New approaches are required to integrate data on symptom severity more effectively into the risk assessment and take account of the severity of certain subjective symptoms, such as abdominal pain. This is required to both protect the allergic consumers who react with severe symptoms to low doses and avoid needless restrictions for foods at which subjects react at low doses but only with mild symptoms.

Clinical implications: Threshold data contribute to the evidence base required to identify levels of allergens below which the majority of patients are unlikely to react, informing allergen risk management plans.

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Supplement E1

1.1 Study Subjects and Exclusion criteria

Study subjects were drawn from the EuroPrevall project as described in Table E1.

Individuals were excluded from undergoing challenges on the basis of the following criteria:

(1) A history of severe life-threatening anaphylaxis occurring within two hours after ingestion of the study food, involving drop in blood pressure, severe bronchospasm or laryngeal edema leading to emergency treatment.

(2) Pregnancy, intake of drugs which might have prevented or aggravated the allergic reaction or which might have interfered with the treatment of a challenge induced allergic reaction as well as any contraindications for the administration of adrenaline (e.g. ischaemic heart disease). I

(3) Patients with ongoing disease which either might have hampered the interpretation of the challenge outcome (chronic urticaria, seasonal allergy during the season) or aggravated the severity of the allergic reaction (acute viral infection, mastocytosis) were not considered for challenges.

A number of patients were excluded from undergoing challenges as they had a history of severe reactions, including anaphylaxis:

peanut: 33; hazelnut: 16; celeriac; 10; fish: 11; shrimp: 13.

1.2 Symptom recording and ranking

Symptoms were ranked in order of severity as adjudged through a consensus meeting of the EuroPrevall clinical partners as described in Table E2.

1.3 Serum IgE measurements

Food specific IgE was determined by ImmunoCAP (ThermoFisher, Uppsala, Sweden) in serum samples from the cohorts using strategies appropriate to the age group and study. For study A serum analyses were performed at the Charité University Medical Center, Germany [1] using ImmunoCAP fx5 (milk, egg, peanut, wheat, fish, soybean) with specific IgE to hazelnut, celeriac or shrimp determined in cases where allergy to these foods was suspected. Serum IgE determination for study B was initially undertaken using a screen comprising five allergen mixes, three of which were prepared specifically for the EuroPrevall study [2, 3] at the Academic Medical Center, Amsterdam. Serological analyses for study C samples were performed at the Paul Ehrlich Institute, Langen, Germany against 24 foods including peanut, hazelnut, celery, fish and shrimp, 12 common inhalant allergen sources and latex [2]. A positive test was designated by ≥ 0.35 kUA/l of specific IgE; where mixes tested positive repeat analysis was undertaken for individual foods.

1.4 Oral Food Challenge Materials

The allergenic ingredients used for DBPCFC were peanut (mechanically defatted lightly roasted peanut flour), hazelnut (hazelnut flour), cod (freeze-dried cod powder, prepared for EuroPrevall by Dr Joyce Boye, Agri-Food Canada), shrimp (frozen North Atlantic prawns) and celeriac (celeriace powder, and available as a food ingredient termed as celery spice powder). Allergenic ingredients were formulated either in a dessert product for young children (Sinlac® Nestlé) to which orange food colouring was added (population A), or the EuroPrevall chocolate dessert [4] with the top dose for peanut and hazelnut delivered in a chocolate bar to maintain blinding (studies B and C; [5]). An extended dose range was required for shrimp which was served as a burger formed with chicken with tomato sauce, based on a recipe provided by Professor Steve Taylor at the University of Nebraska.

1.5 Dosing schedules used in double blind placebo controlled food challenge.

All the challenges used a low-dose protocol but in some instances there were differences in exact dose progressions in the challenge used depending on the study and food. Furthermore, as the challenge studies were undertaken it became apparent that the dosing protocols for fish, and particularly shrimp, had to be amended as study participants were reacting at much higher doses than had originally been anticipated. Thus the fish protocol employed in study A commenced with a dose of 11.5µg protein (Table E2). The study A protocols were applied in young children in studies B and C, together with three other dosing protocols were used for fish and four different protocols for shrimp in studies B and C (Table E3) where amendments were made to increase the amounts given in the final doses which allowed 12g fish (fish protocol 2) and 9g of shrimp (shrimp protocol 4).

1.6 Placebo Reactions

A number of individuals experienced reactions when receiving the placebo arm of the DBPCFC. These are summarised in Table 1 of the main manuscript. The details of individuals experiencing placebo reactions are given in Table E3 and which were excluded from all further analysis.

1.7 References

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On line Supplementary Figure Legends

Figure Suppl 1: Dose distributions for reactions to hazelnut modelled using interval censoring survival analysis fitted with lognormal [black], loglogistic [green] and weibull [red] dose distributions. Open circles: NOAEL; Closed circles: LOAEL; censored intervals shown as a pair of linked open and closed circles; single open (closed) circles are NOAELs (LOAELs) of right-(left-) censored observations.

Figure Suppl 2: Dose distributions for reactions to peanut modelled using interval censoring survival analysis fitted with lognormal [black], loglogistic [green] and weibull [red] dose distributions. Open circles: NOAEL; Closed circles: LOAEL; censored intervals shown as a pair of linked open and closed circles; single open (closed) circles are NOAELs (LOAELs) of right-(left-) censored observations.

Figure Suppl 3: Dose distributions for reactions to celery modelled using interval censoring survival analysis fitted with lognormal [black], loglogistic [green] and weibull [red] dose distributions. Open circles: NOAEL; Closed circles: LOAEL; censored intervals shown as a pair of linked open and closed circles; single open (closed) circles are NOAELs (LOAELs) of right-(left-) censored observations.

Figure Suppl 4: Dose distributions for reactions to fish modelled using interval censoring survival analysis fitted with lognormal [black], loglogistic [green] and weibull [red] dose distributions. Open circles: NOAEL; Closed circles: LOAEL; censored intervals shown as a pair of linked open and closed circles; single open (closed) circles are NOAELs (LOAELs) of right-(left-) censored observations.

Figure Suppl 5: Dose distributions for reactions to shrimp modelled using interval censoring survival analysis fitted with lognormal [black], loglogistic [green] and weibull [red] dose distributions. Open circles: NOAEL; Closed circles: LOAEL; censored intervals shown as a pair of linked open and closed circles; single open (closed) circles are NOAELs (LOAELs) of right-(left-) censored observations.

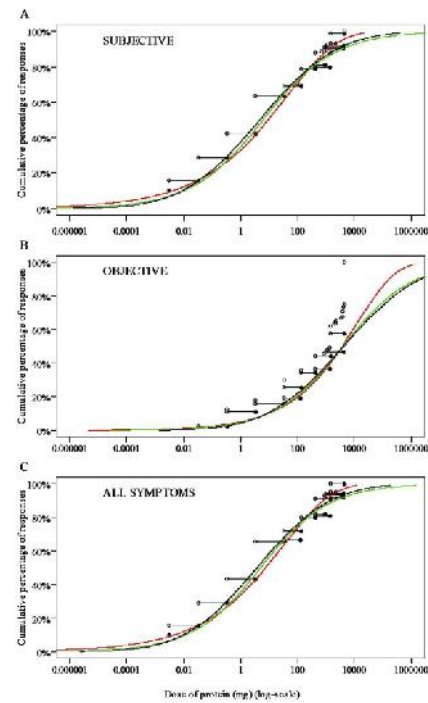


Fig E1

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How much is too much?: Threshold dose distributions for 5 food allergens

Journal of Allergy and Clinical Immunology, 2015

<http://dx.doi.org/10.1016/j.jaci.2014.10.047>

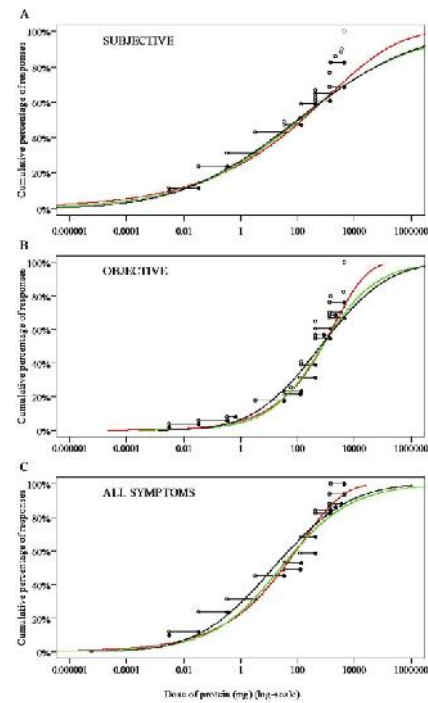


Fig E2

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How much is too much?: Threshold dose distributions for 5 food allergens

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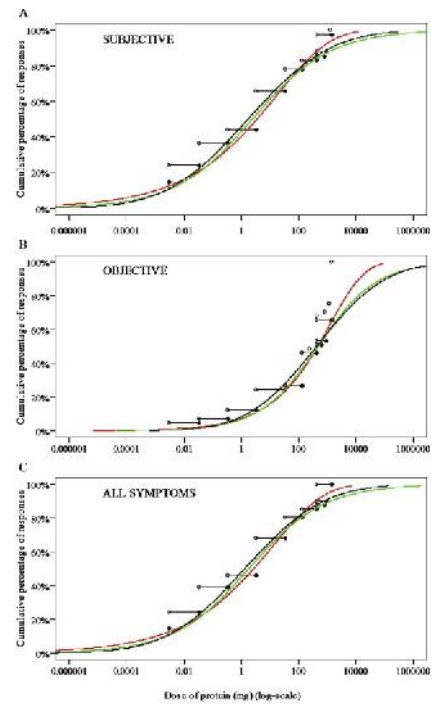


Fig E3

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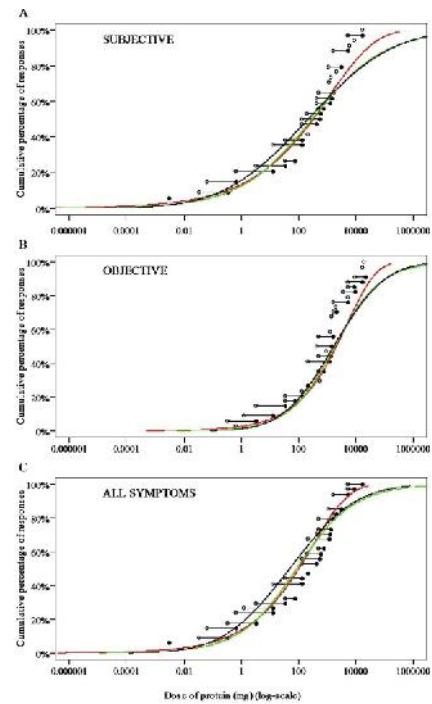


Fig E4

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How much is too much?: Threshold dose distributions for 5 food allergens

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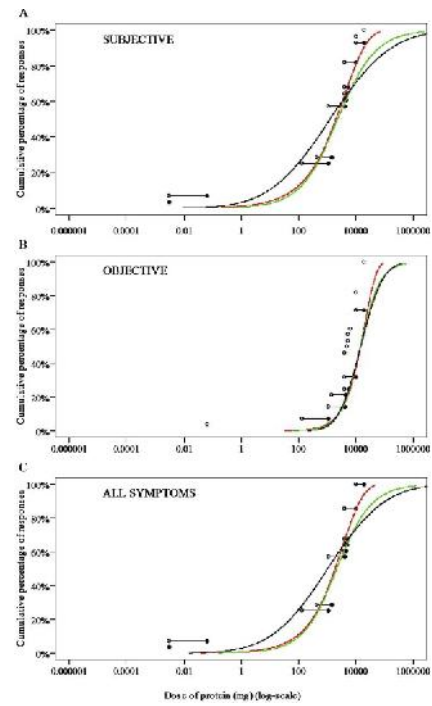


Fig E5

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How much is too much?: Threshold dose distributions for 5 food allergens

Journal of Allergy and Clinical Immunology, 2015

<http://dx.doi.org/10.1016/j.jaci.2014.10.047>

Table E1: Challenge population characteristics [§] Reactive participants used for dose-response modelling. * Participants classified as reactive but experiencing delayed reactions, worsening of eczema (D-AD), and other reactions (O) that could not be linked to challenge doses and were excluded from dose response modelling. Ages are given in years as medians of each population. The population of food allergic individuals who underwent DBPCFC (Table E1 in this article's Online Repository) came from the EuroPrevall birth cohort (A), those having probable food allergies from the EuroPrevall community surveys in adults and school-age children (B) and an outpatient clinic population (C).

Food	Total Population			Total Reactive Population			Reactive (Reference) Population [§]			Reactive (Other) Population*			Tolerant			Placebo Reactor							
	No	No /Study		Age	No	%	Age	No	No/Study		Age	No	No/Study		Age	No	No/Study		Age	No	No/Study		Age
		A	B+C						A	B+C			A	B+C			A	B+C					
Hazelnut	132	5	127	30.8	91	68.9	31.6	90	3	87	31.6	1	0	1 (O)	36.4	24	2	22	28	17	0	17	25.6
Peanut	135	60	75	10.4	60	44.4	7.6	51	20	31	14.9	9	4 (D, AD) 4 (O)	1 (O)	2.2	62	31	31	6.1	13	1	12	25.2
Celeriac	64	0	64	32.2	41	64.1	30.1	41	0	41	30.1	0	0	0	N/A	19	0	19	34.8	4	0	4	41.1
Fish	50	13	37	14.2	34	68.0	12.3	34	11	23	12.3	0	0	0	N/A	12	2	10	13.0	4	0	4	35.3
Shrimp	55	0	55	30.8	30	54.5	31.7	28	0	28	32.1	2	0	2 (O)	35.7	20	0	20	30.8	5	0	5	11.0
Total	436	78	358	23.7	256	59	22.6	244	34	210	24.2	12	8	4	24.7	137	35	102	22.5	43	1	42	27.6

Supplement Table E2: Double blind placebo controlled food challenge dosing schedules used in study A (EuroPrevall Birth Cohort)

Dose Number	Protein dose (mg)	
	Peanut and Hazelnut	Fish
Dose 1	0.003	0.0115
Dose 2	0.03	0.115
Dose 3	0.3	1.115
Dose 4	3	11.5
Dose 5	30	115
Dose 6	90	345
Dose 7	300	1200
Dose 8	900	3500
Dose 9	3000	11500

Supplement Table E3: Double blind placebo controlled food challenge dosing schedules used in studies B (community survey) and C (outpatient clinical study).										
Dose No	Protein dose (mg)									
	Peanut	Hazelnut	Celeriac	Fish (1)	Fish (2)	Fish (3)	Shrimp (1)	Shrimp (2)	Shrimp (3)	Shrimp (4)
Dose 1	0.003	0.003	0.003	0.003	0.003	0.003	0.003	0.6	0.003	0.003
Dose 2	0.03	0.03	0.03	0.03	0.06	0.06	0.06	12	0.03	0.06
Dose 3	0.3	0.3	0.3	0.3	0.6	0.6	0.6	120	0.3	0.6
Dose 4	3	3	3	3	12	12	12	6.2	3	12
Dose 5	30	30	30	30	56	120	120	44.7	30	120
Dose 6	100	100	100	100	120	1000	1000	931.7	100	1000
Dose 7	300	300	300	300	400	2000	3000	2980	300	3000
Dose 8	1000	1000	1000	1000	880	6000			1000	6000
Dose 9	3000	3000			2000	12000			3000	9000
Dose 10					6000					

Supplement Table E4: Symptoms recorded during challenges in rank order of severity where (1) is the least severe

Rank Order	Symptom	Abbreviation	Objective (O)/ Subjective (S)
1	Oral Allergy Syndrome, defined within the study context as itching of the oral mucosa after contact with food, which is independent of the pathogenesis and is not necessarily “pollen-related”	OAS	S
2	Blister of the oral mucosa	B,	O
3	Localised pruritus [study A only]	Lpru	S
4	Generalised pruritus [study A only]	Gpru	S
5	Rhinitis	R	O
6	Conjunctivitis	C,	O
7	Dysphagia	Dph	S
8	Nausea,	N	S
9	Flush	F	O
10	Urticaria	U,	O
11	Cough	Co	O
12	Dyspnea	D	O (Study A) S (Study B,C)
13	Angioedema	AE	O
14	Gastric pain and/or burning	G	S
15	Emesis	E	O
16	Diarrhoea	Di	O
17	Laryngeal oedema	L	O
18	Bronchospasm,	BS	O
19	Drop of blood pressure	BP	O
2-	Shock	S	O