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Quantitative risk reduction through peanut immunotherapy: Safety benefits of an increased threshold in Europe

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Abstract

Background: The clinical relevance of increasing an allergic individual's peanut sensitivity threshold by immunotherapy, that is, eliciting dose (ED) to 300 or 1000 mg peanut protein, has not been previously characterized in a European population. In this study, we quantify the clinical benefits of an increased threshold of reaction following immunotherapy for the peanut-allergic individual.

Methods: Quantitative risk assessments incorporated numerous inputs to predict the risk of an allergic reaction after exposure to residual peanut protein in packaged foods. The three primary inputs for the risk assessment were the peanut-allergic individual's clinical threshold value, the amount of food consumed per eating occasion of selected packaged foods, and the concentration of peanut protein in the consumed product. Individual risk reductions were calculated for both children and adolescents-adults.

Results: Using available consumption and packaged food contamination data, children reaching an ED of 300 mg (if initial ED ≤ 100 mg) or 1000 mg (if initial ED 300 mg) achieved >99.99% risk reduction. Adolescents-adults also achieved >99.99% risk reduction in all cases but one. Adolescents-adults who reached an ED of 300 mg (if initial ED ≤ 100 mg) achieved 99.3%-99.9% risk reduction when consuming ice cream.

Conclusions: It is concluded that an increase in threshold following immunotherapy which achieves an eliciting dose of 300 or 1000 mg peanut protein is clinically relevant for the European peanut-allergic population. Benefits of an increased threshold include a significant reduction in risk due to traces of peanut protein.

KEYWORDS

efficacy, immunotherapy, peanut allergy, risk reduction, risk/Benefit Analysis

1 | INTRODUCTION

Peanut allergy is a generally persistent, sometimes life-threatening food allergy that is increasing in prevalence in Western countries.[1,2] Several studies have investigated individual thresholds and the population threshold for allergic reactions to peanut through double-blind, placebo-controlled food challenges (DBPCFC) and shown that allergic reactions can be caused by miniscule amounts of peanut protein.[3-6] Current management strategies for peanut allergy are limited to strict avoidance of peanut consumption and use of rescue medication upon symptoms due to unintentional peanut ingestion.[7,8] However, complete avoidance of peanut is difficult due to its widespread use as a food ingredient in packaged foods and in restaurant or catering meals.

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Unexpected allergic reactions to food and to peanut in particular are frequent, occur in nearly half of food-allergic patients and symptoms can be mild, moderate and severe.[9-12] Packaged food products do on occasion contain unintended allergen residue despite efforts to minimize cross-contact[13-16] and a recent Dutch study following allergic patients found that packaged foods were the main cause of unexpected reactions.[11] In a number of instances, food manufacturers utilize "may contain" precautionary allergen labeling (PAL) as a voluntary measure to communicate potential risk to allergic consumers. However, inconsistent application of PAL by the food industry and a disconnect between the presence or absence of PAL and the actual risk of the product have led to a loss of trust in PAL, consumption of PAL labeled products, and increased risk-taking by allergic consumers.[17,18] Multiple studies report baseline risks of allergic reactions in peanut-allergic consumers of certain product categories to be between 1% and 3% after accounting for frequency of contamination, for both products without mention of peanut on the label, and for products containing PAL for peanut.[14,19-21] Additionally, when researching unexpected allergic reactions, Michelsen et al[11] reported that the allergen was not mentioned as an ingredient or warning on the labels in 37% of the cases, indicating that 63% of the reactions were caused by products with the allergen of interest on the label and could be the result of increased risk-taking behavior due to frustrations with PAL.

To date there are no approved therapeutic interventions for peanut allergy or any food allergy. However, recent reviews highlight the development and potential of immunotherapy as an active form of treatment and disease-modifying therapy for peanut allergy.[22-24] Different forms of immunotherapy trials exist including oral, sublingual or epicutaneous and all have an efficacy endpoint of an increased individual threshold (eliciting dose) or the cumulative reactive dose tested during DBPCFC. Desensitization results for peanut have shown good efficacy for increasing an individual's threshold with a good safety profile but the ability of immunotherapy to induce long-term tolerance needs further study.[22-24] It has been demonstrated that a history of more severe reactions due to accidental allergen exposure or lower tolerated doses during food challenge was indicative of a significantly lower QOL in children.[25] Thus, an increase in threshold following immunotherapy in a food-allergic individual who initially had a low threshold can have a significant impact on that food-allergic individual's quality of life, as well as their caretakers.

A recent study by Baumert et al[26] aimed to quantitatively demonstrate the clinical benefits of increasing an individual's threshold through immunotherapy in the American population. A >95% reduction in reaction risk was demonstrated, across packaged food categories, for the peanut-allergic individual who achieved a threshold of 300 mg peanut protein or more after immunotherapy. It was concluded that an increase in an individual threshold from 100 mg or less to 300 mg peanut protein or more is a clinically meaningful endpoint and a relevant objective for peanut immunotherapy.[26] Increasing one's individual threshold to 300 mg peanut protein or higher could have a significant impact on the number of unexpected allergic reactions from consumption of packaged foods contaminated with peanut as prior DBPCFC research has indicated that without immunotherapy, >65% of the peanut-allergic population would be predicted to experience an allergic reaction when exposed to 300 mg peanut protein.[7] Further, >80% of the peanut-allergic population would be predicted to experience an allergic reaction when exposed to 1000 mg peanut protein.[7]

In this study, we applied quantitative (probabilistic) risk modeling using food consumption data from the 2007-2010 Dutch National Food Consumption Survey (DNFCS) and the EFSA Comprehensive European Food Consumption Database to determine the clinical relevance of increasing an individual's threshold through immunotherapy in a European population. We report and quantify the probability of an allergic reaction for given thresholds due to the unintended presence of peanut protein in packaged food products, as well as the protective nature and reduction of risk due to increasing one's individual threshold through immunotherapy. It is not the focus or intention of our study to examine the safety or efficacy of immunotherapy treatments and future research could be directed to assess the risk reduction by specific immunotherapy treatments through the application of data from recent and ongoing clinical trials.

2 | METHODS

2.1 | Input parameters for quantitative risk assessment

The overall quantitative risk assessments performed in this study incorporated a wide range of input variables in order to predict the risk of an allergic reaction after exposure to residual peanut protein in packaged food products. The three primary inputs for the risk assessment were the peanut-allergic individual's clinical threshold value, the concentration of peanut protein in the consumed food product, and the amount of food consumed per eating occasion of selected packaged food products. The overall study design and simulation methods for studying quantitative risk reduction through immunotherapy in a food-allergic population were detailed previously by Baumert et al[26] for the US population and are briefly described below as adapted for the current study.

2.2 | Peanut-allergic individual clinical threshold amounts

A series of individual quantitative risk assessments were conducted through utilization of a constant individual clinical threshold of 1, 3, 10, 30, 100, 300, or 1000 mg of peanut protein. These clinical threshold values were representative of mg protein amounts in the joint American and European guidelines for DBPCFCs[27] as well as a number of other known dosing schemes for food challenges. Additionally, this range of doses is also representative of the

individual thresholds doses for peanut-allergic individuals in graded food challenges.[7]

Post simulation comparison of results for the probability of an allergic reaction for an individual with a threshold of 1 mg of peanut protein vs a threshold of 100, 300, or 1000 mg of peanut protein (for example) allows for calculation of the quantitative risk reduction values for an individual consuming package food products and who has achieved an increased threshold of reaction following immunotherapy.

2.3 | Concentration

The concentration of unintended peanut protein found in packaged food products for this study was selected randomly from the semi-logarithmic distribution of 1, 3, 10, 30, 100, 300, and 1000 ppm (mg/kg) of peanut protein.

These values were selected after careful study of European and North American retail surveys and governmental sources regarding the unintended presence of peanut in packaged foods and are representative of the wide distribution of peanut protein in these studies.[13,15,16,19,21,26,28-33] The contamination levels reported on European food products were highly comparable with those obtained from US food products, indicating that for the European situation a concentration distribution for 1 to 1000 ppm (mg/kg) would be appropriate. After careful study of the contaminated foods in the available packaged food studies, five food groups were selected for use in the current project (cookies, croissants, doughnuts, ice cream, salty snacks).

As the concentration of peanut protein was randomly selected per iteration of the simulation, this resulted in an equal distribution of concentration values. However, the distribution of concentrations of unintended peanut protein in retail surveys of packaged foods is primarily in the range of 1-30 ppm of peanut protein. Additionally, 100% of products in our study were assumed to contain unintended peanut protein where <10% of packaged foods in the abovementioned studies contained detectable concentrations of peanut. Therefore, it was expected that the concentrations of unintended peanut protein in our simulation were overly conservative when compared to the results of retail surveys in published literature. This overestimate regarding the concentration of peanut allows us to conservatively estimate the probability of a peanut-allergic individual reacting to a contaminated product and to estimate risk reductions due to an increased threshold of reaction following immunotherapy. Due to the relative nature of risk reduction comparisons, it should be noted that the overestimation of the peanut concentration and conservative absolute risk does not lead to an overestimation of the risk reduction after immunotherapy.

2.4 | Consumption data for product categories

Dutch consumption data were obtained from the Dutch National Food Consumption Survey (DNFCS) of the National Institute of Public Health and the Environment. The food products found within the 2007-2010 DNFCS database have been labeled with the common European Food Safety Authority (EFSA) food codes for consumption surveys (FoodEx2),[34] and five food groups were used in the current project (cookies, croissants, doughnuts, ice cream, salty snacks). Detailed food codes and categories for this study can be found in Tables S1-S5.

Consumption of two age-groups was studied separately, children (7-11 years) and adolescents-adults (12-69 years). Additionally, the individual food codes within the five Dutch food categories were chosen to match US food categories previously analyzed by Baumert et al[26] as closely as possible to enable study comparison. Doughnuts are widely consumed in the USA but are found less often in European supermarkets or bakeries. Therefore, croissants were included as a food group in this analysis due to a possible low consumption of doughnuts in Europe. Consumption estimates during the simulations included the entire range of reported gram amounts consumed per eating occasion by participants in the DNFCS (ie, breakfast, lunch, dinner, and other distinct eating occasions during the day). In the case of multiple consumptions of a food category by a single participant, the maximum reported consumed amount was used for the utilized. These methods are considered both conservative and reflective of consumption trends in the Dutch population.

Additionally, reported daily mean consumption estimates from 22 countries with children and adults consuming ice cream or cookies in the EFSA Comprehensive European Food Consumption Database[35] were analyzed with the maximum reported intake utilized for a conservative consumption estimate across European countries.

2.5 | Quantitative risk assessment

As previously described by Baumert et al[26] the Monte Carlo-based risk model simulated 100 000 eating occasions through a random selection and calculation of exposure doses compared with a constant threshold dose of 1, 3, 10, 30, 100, 300, or 1000 mg of peanut protein to determine whether there was a risk of an allergic reaction. The risk model calculated a mg exposure amount of peanut protein through a random selection of the concentration of peanut residue (1, 3, 10, 30, 100, 300, and 1000 ppm of peanut protein) and pairing this with a randomly selected consumption value from the reported consumed amounts per eating occasion in the DNFCS for each product category. An allergic reaction was predicted to occur if the exposure dose (mg of peanut protein) was greater than the individual threshold dose (mg of peanut protein). This process of simulating 100 000 eating occasions was then repeated 50 times for a total of 5 000 000 simulated eating occasions for each individual threshold value across two age-groups, children (7-11 years) and adolescents-adults (12-69 years). The overall approach of this study is outlined in Figure 1.

The results of this study are presented as the peanut-allergic individual risk or the probability of a reaction occurring when it is

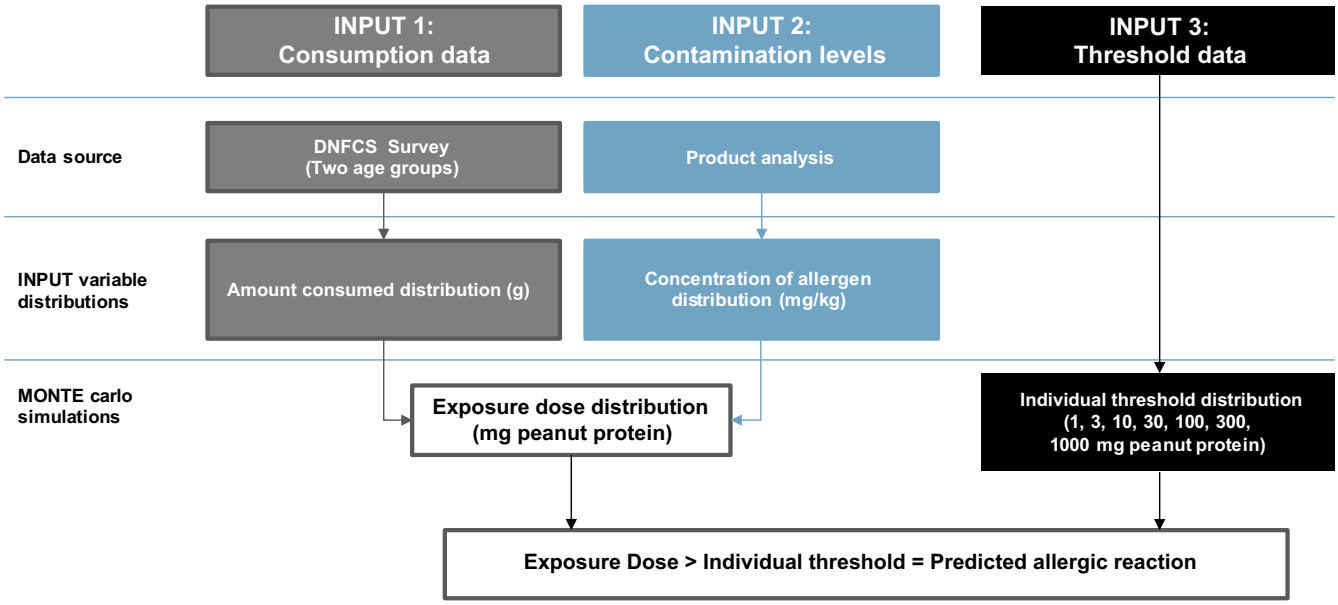

FIGURE 1 Quantitative risk assessment approach for the current study [Colour figure can be viewed at wileyonlinelibrary.com]

conservatively assumed that all individuals are peanut-allergic and all consume a product that contains unintended peanut residue during every eating occasion. In previous studies, this was presented as the peanut-allergic user risk.[13,19,32]

It is well understood that peanut-allergic individuals are not likely to consume of the selected product categories during every eating occasion, and thus, the risks in everyday life would be lower than those presented in this study. However, these over-conservative estimations do allow for the calculation of predicted decrease in risk when consuming a contaminated packaged food product due to an increased threshold of reaction following peanut immunotherapy.

2.6 | Risk reduction calculation

The reduction in risk of a predicted allergic reaction due to an increased threshold of reaction following immunotherapy can be expressed as a percentage decrease in risk to further examine the benefits of an increased threshold. The percentage decrease in risk was calculated using the percentage of predicted reactions and using the following formula:

$$\left(1-\frac{\text{Risk at POST–immunotherapy mg peanut protein threshold}}{\text{Risk at baseline PRE–immunotherapy mg peanut protein threshold}}\right)\times 100\% = \text{Percentage decrease in risk (\%)}$$

3 | RESULTS

In order to quantify the risk reduction in a European population consuming packaged foods due to an increased threshold of reaction following immunotherapy, we first had to assess the risk of five packaged food product categories (cookies, croissants, doughnuts, ice cream, salty snacks) using consumption data from the DNFCS. The summary statistics (mean, 90th percentile, 95th percentile, maximum) for consumption per eating occasion are presented in Table 1 for children (7-11 years) and adolescents-adults (12-69 years) for each product category. Ice cream was the highest consumed product on a population basis for both children and adolescents-adults. Unsurprisingly, across all product categories, the maximum amount consumed in a single eating occasion was higher for adolescents-adults than for children. The average amount consumed was higher in the adolescents-adult population in all product categories except for cookies. Simulated consumption summary statistics from risk assessments performed in this study can be found in Table S6 and closely match the sampled consumptions from Table 1.

The percentage of eating occasions predicted to result in an allergic reaction for each of the selected products and age-groups is presented in Table 2. As expected from the consumption results, adolescents-adults are predicted to have a slightly higher risk compared to children with a similar peanut protein threshold value for all of the product categories except for cookies, where children have the slightly higher risk. Croissants were included in the current study due to a prestudy assumption of a possible low number of consumer of doughnut in a European population. However, doughnuts or similar products were reported as consumed frequently enough in the Dutch population to continue with further risk assessments. The consumption distributions of croissants and doughnut within the DNFCS dataset were similar (Table 1) and thus led to a similar number of predicted allergic reactions (Table 2), although the maximum consumption of doughnuts is higher and leads to a slightly higher predicted risk than croissants in individuals with a 100 mg peanut protein threshold.

TABLE 1 Consumption summary statistics for children (7-11 y) and adolescents-adults (12-69 y) in 2007-2010 Dutch National Food Consumption Survey (DNFCS)

	N	Mean (g)	Standard deviation (g)	P90 (g)	P95 (g)	Max (g)
Cookies						
Child	591	36.8	21.1	59	72	135
Adolescent-adult	1922	34.7	23.0	59	70	225
Croissants						
Child	67	53.1	23.7	80	94	120
Adolescent-adult	217	65.2	34.8	120	144	240
Doughnuts						
Child	35	50.9	24.8	70	91.4	140
Adolescent-adult	74	74.9	52.1	138.5	185.5	285
Ice cream						
Child	273	71.5	29.8	105	120.8	183
Adolescent-adult	573	93.5	45.0	150	183	330
Salty snacks						
Child	90	29.4	17.5	53.3	59	100
Adolescent-adult	258	40.1	30.5	79	100	175

In a number of instances, no allergic reactions were predicted due to the maximum consumption amount in the DNFCS limiting the exposure to values below the highest threshold, even when 1000 ppm peanut protein was present in the product. This is logical as an individual with a 1000 mg peanut protein threshold would need to consume 1000 g or more of a product containing 1000 ppm peanut protein in order to exceed their threshold. Consumption instances of greater than 1000 g were not reported in the DNFCS for the selected packaged food categories. Thus, an individual with a 1000 mg peanut protein threshold was not predicted to be at risk of a reaction based on the reported DNFCS data. A number of reasons, including underreporting, could contribute to no reported consumption instances above 1000 g, but one should also consider the use of smaller single- or multiserve containers for packaged foods that do not contain 1 kg of product, the airy nature of wheat-based cookies, croissants, doughnuts, and salty snacks limits the weight of the

TABLE 2 Risk assessment results for children (7-11 y) and adolescents-adults (12-69 y) presented as the percentage of eating occasions predicted to result in an allergic reaction

Peanut-allergic individual's threshold value	Age-group	Cookies[a] (%)	Croissants[a] (%)	Doughnuts[a] (%)	Ice cream[a] (%)	Salty snacks[a] (%)
1	Children	49.3	56.3	56.3	58.3	45.9
	Adolescents-adults	48.2	58.2	59.3	60.6	48.9
3	Children	35.2	42.0	42.0	44.2	31.6
	Adolescents-adults	34.2	43.9	45.0	46.4	34.8
10	Children	20.8	27.7	27.8	29.7	17.6
	Adolescents-adults	19.7	29.6	30.7	32.1	20.5
30	Children	7.6	13.9	13.5	15.6	5.1
	Adolescents-adults	7.0	15.6	16.4	17.9	7.6
100	Children	0.34	0.63	0.82	1.57	NR
	Adolescents-adults	0.21	1.86	2.90	3.76	0.56
300	Children	NR	NR	NR	NR	NR
	Adolescents-adults	NR	NR	NR	0.0257	NR
1000	Children	NR	NR	NR	NR	NR
	Adolescents-adults	NR	NR	NR	NR	NR

NR, No reaction predicted.

[a]A 100% of food products were assumed to contain unintended peanut residue randomly selected from the concentration range from 1, 3, 10, 30, 100, 300, or 1000 ppm peanut protein.

product or the general physiological limitations regarding the size of a human stomach. Similarly, an individual with a 300 mg peanut protein threshold would need to consume 300 g or more of a product containing 1000 ppm peanut protein to exceed their threshold dose, an instance which was only reported to occur for adolescents-adults consuming ice cream based on the DNFCS survey data. Thus, a reaction was only predicted to occur if the maximum consumer of ice cream was peanut-allergic and the ice cream contained a worst-case concentration of peanut.

The reduction in risk of a predicted allergic reaction due to an increased threshold of reaction following immunotherapy can be expressed as a percentage decrease in risk to further examine the benefits of an increased threshold. The percentage decrease in risk was calculated using the percentage of predicted reactions in Table 2. For example, an adult consumer of cookies with a baseline threshold of 1 mg peanut protein pre-immunotherapy that increases their threshold to 100 mg post-immunotherapy decreases their risk of allergic reaction from 48.2% to 0.21% (Table 2), which corresponds to a decrease in risk 99.6%.

$$\left(1-\frac{0.21}{48.2}\right)\times 100\% = 99.6\% \text{ decrease in risk}$$

Adult consumers of cookies that increased their threshold to 300 or 1000 mg peanut protein were not predicted to have an allergic reaction and had a decrease in risk of >99.99% within our study. Further calculations of the decrease in risk are presented in Table 3 for children and adolescents-adults consuming cookies or ice cream, two of the respective food product categories with the highest and lowest risk reduction percentages. Decrease in risk calculations is presented for all product and age combinations in Figure S1.

As shown in Table 3, children who reach a post-immunotherapy individual threshold value of 100 mg peanut protein experienced a risk reduction of 90.0%-99.3% (>99.99% risk reduction for from salty snack consumption due to no predicted risk in the current simulation), while comparable adolescents-adults experienced a risk reduction of 78.9%-99.6% depending on their pre-immunotherapy threshold value and product being consumed. In the current simulation, individuals who achieved a post-immunotherapy individual threshold value of 300 mg peanut protein or more were no longer predicted to be at risk of an allergic reaction due to unintentional peanut protein in the selected packaged foods for all age and product combinations (>99.99% risk reduction), except one. In this case, adolescents-adults who reached an ED of 300 mg (if initial ED ≤ 100 mg) achieved 99.3%-99.9% risk reduction when consuming ice cream. Adolescents-adults consuming ice cream that achieved a post-immunotherapy threshold of 1000 mg peanut protein were no longer predicted to be at risk of an allergic reaction (>99.99% risk reduction).

A post-immunotherapy threshold of 300 mg peanut protein or higher provides a clear reduction in the risk of experiencing an allergic reaction due to the unintended presence of peanut for children and adolescents-adults consuming the selected packaged food product categories of cookies, croissants, doughnuts, ice cream, and salty snacks. Additionally, even when statistical distributions were fit to the reported DNFCS consumption values (ie, lognormal or Weibull) and maximum consumption amounts outside of the realistic range were generated (ie, 3087 g consumption of salty snacks, equivalent to 6-7 family size bags of tortilla chips, or a 2652 g consumption of doughnuts, equivalent to more than 35 individual doughnuts), there was still a calculated risk reduction of 97.3%-99.99% when an individual reaches a 300 mg threshold after immunotherapy (data not shown). These results further indicate that reaching a threshold of 300 mg peanut protein or higher after immunotherapy provides a clear protection and reduction of risk of possible consumptions outside of the DNFCS reported values.

Throughout Europe, adults eating ice cream in different consumption surveys reported a mean daily consumption of 98 g/day (interquartile range of 80-112 g/day, minimum of 74 g/day [The Danish National Dietary survey 2005-2008], maximum of 152 g/day [Austrian Study on Nutritional Status 2005-06]) in comparison with the DNFCS data estimates a consumption amount of 93.5 g/eating occasion for adults eating ice cream. Results from the available data indicate that consumption amounts are similar across Europe for the packaged foods in this study (Figure S2). As an added measure of conservatism to ensure applicability of the results across Europe, an additional quantitative risk assessment was conducted to simulate the highest intake ice cream consumption scenario across European countries. The simulation was done by generating similar consumptions to those reported in the Austrian Study on Nutritional Status (2005-06) and the Estonian National Dietary Survey (1997), the two countries reporting the highest daily consumptions of milk-based ice cream by European adults. Reported average daily consumptions of milk-based ice cream was 152 g/day in Austria and 151 g/day in Estonia, with both countries reporting a 99th percentile of consumption as 500 g/day. As detailed individual data for Austria and Estonia were not available to the authors, data from the adolescents-adults (12-69 years) reporting the consumption of ice cream in the Dutch National Food Consumption Survey were used with an additional a multiplication factor of 160% applied to each eating occasion for a mean consumption of 150 g/eating occasion and a maximum eating occasion of 528 g, indistinguishable from the estimates for the maximum reported daily consumptions of ice cream in Europe. In this maximum ice cream consumption simulation, individuals reaching a post-immunotherapy individual threshold value of 300 mg peanut protein experienced a predicted 96.3%-99.4% reduction in risk of an allergic reaction due to unintentional presence of peanut (Figure S3). These conservative consumption amounts for packaged foods cover the entire relevant range of reported consumptions across Europe for the five packaged foods of interest (cookies, croissants, doughnuts, ice cream, and salty snacks). Therefore, it is possible to foresee the protective benefits of peanut immunotherapy demonstrated in this study applying to the larger European population of peanut-allergic individuals.

TABLE 3 Risk reduction calculations for children and adolescents-adults consuming cookies or ice cream due to an increase in threshold

Cookies - Children		Threshold Dose – Post-Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	28.5%	57.9%	84.5%	99.3%	>99.99%	>99.99%
	3		0.0%	41.1%	78.3%	99.0%	>99.99%	>99.99%
	10			0.0%	63.2%	98.4%	>99.99%	>99.99%
	30				0.0%	95.6%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Cookies - Adolescents-adults		Threshold Dose – Post-Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	29.1%	59.2%	85.4%	99.6%	>99.99%	>99.99%
	3		0.0%	42.4%	79.4%	99.4%	>99.99%	>99.99%
	10			0.0%	64.3%	98.9%	>99.99%	>99.99%
	30				0.0%	97.0%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Ice Cream - Children		Threshold Dose – Post-Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	24.2%	49.0%	73.2%	97.3%	>99.99%	>99.99%
	3		0.0%	32.7%	64.6%	96.4%	>99.99%	>99.99%
	10			0.0%	47.4%	94.7%	>99.99%	>99.99%
	30				0.0%	90.0%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Ice Cream - Adolescents-adults		Threshold Dose – Post-Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	23.4%	47.1%	70.6%	93.8%	99.9%	>99.99%
	3		0.0%	30.9%	61.6%	91.9%	99.9%	>99.99%
	10			0.0%	44.3%	88.3%	99.9%	>99.99%
	30				0.0%	78.9%	99.9%	>99.99%
	100					0.0%	99.3%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

These food product categories were selected as examples with the highest and lowest risk reduction percentages, dependent on the age-group. Decrease in risk calculations is presented for all product and age combinations in Figure S1 [Colour figure can be viewed at wileyonlinelibrary.com]

4 | DISCUSSION

The desire to avoid potential life-threatening symptoms due to unintentional, accidental ingestion of allergens in the "uncontrolled" environment of everyday life is the main motivation of peanut-allergic individuals to be enrolled in an immunotherapy study.[36] Therefore, the results of immunotherapy trials should be analyzed with these thoughts in mind.

Baumert et al[26] were the first to quantify the level of protection inferred by a clear increase in threshold during peanut immunotherapy against allergic reactions to food products that contain trace amounts of peanut. The work of Baumert et al[26] focused on the US population, and the current study is the first to quantify the level of protection provided by peanut immunotherapy in a European population. Methods of the current study were designed in a similar fashion to Baumert et al[26] with the intention of comparing previous results to the level of protection inferred in a European population. Accordingly, food categories were chosen for the current study to match US food categories previously analyzed and results of the two studies were similar on a number of levels. Even though Baumert et al[26] did not split consumption into separate age-groups, the reported consumption trends between the USA and the Netherlands were comparable. The average grams consumed across food categories in the US values were closer to the Dutch adult age-group than children, but both age-groups were still comparable. Average consumption in both studies was highest for ice cream followed by doughnuts/snack cakes/croissants and then cookies or salty snacks. Interestingly, the USA reported higher average amounts of ice cream consumed and the maximum gram amount consumed was larger in the USA for all product categories. One reason for higher amounts of ice cream consumed could be the container sizes available in different countries, with larger multiserve buckets available in the USA compared with smaller multiserve containers in Europe. Availability of similar, larger multiserve or family packages in the USA could also be a reason for the higher maximum reported consumption across food categories when compared to the Dutch market. As expected with comparable average consumption values, similar risks were found for individuals with identical peanut protein threshold values in both studies. For example, individuals with a peanut protein threshold value of 10 mg were predicted to have an allergic reaction 27.5% of the time in the USA and 30.7% in Dutch adolescents-adults, when consuming doughnuts. Due to the higher maximum consumptions reported in the USA, individuals in the USA with a peanut protein threshold of 300 mg were still at a very small risk for an allergic reaction for all product groups while ice cream was the only product group with predicted reactions for similar individuals in the Netherlands. In the current study, as well as,[26] a post-immunotherapy threshold of 300 mg peanut protein provided a relevant reduction in the risk of experiencing an allergic reaction due to the unintended presence of peanut. With the exception of adolescents-adults consuming ice cream, individuals reaching a post-immunotherapy individual threshold value of 300 mg peanut protein or more were no longer predicted to be at risk of an allergic reaction due to unintentional peanut protein in the current study (>99.99% risk reduction), whereas similar individuals in[26] experienced a 94.9%-99.9% reduction in risk across product categories.

While much of the focus from this study could be placed on individuals being able to achieve a reduction in risk of 99% or greater, it should also be noted that children or adults with a pre-immunotherapy threshold of 1 mg peanut protein already benefit from a reduction in risk of >50% in most scenarios if they are able to reach a post-immunotherapy individual threshold of 10 mg peanut protein. Children and adults with a pre-immunotherapy threshold of 1 or 3 mg peanut protein and who are able to achieve a post-immunotherapy threshold of 30 mg peanut protein have a predicted reduction in risk of 61.6%-88.9% depending on the product being consumed. Finally, children who reach a post-immunotherapy individual threshold value of 100 mg peanut protein experienced a risk reduction of 90.0%->99.99% and comparable adolescents-adults experienced a risk reduction of 78.9%-99.6% depending on their pre-immunotherapy threshold value and product being consumed. So while it is clear that a reduction in risk of 99.9% is clinically relevant, a reduction in risk of 50%-85% could also already be clinically relevant for the most highly sensitive peanut-allergic individuals.

Avoidance of peanut is only an effective risk management strategy when peanut is clearly identifiable in packaged food products. However, that is not always possible as packaged foods with and without PAL can contain similar concentrations of an unexpected allergen[13,19] and cause allergic reactions.[11] The reduction in risk due to an increased threshold during immunotherapy provides a clear, clinically significant benefit to the allergic individual seeking to avoid a reaction due to accidental ingestion of allergens when consuming packaged foods. Still, it must be noted that our study is limited in scope to selected packaged food products and does not allow and peanut-allergic individuals who have achieved a threshold dose of 300 mg of peanut protein to become less diligent with their peanut avoidance diet. There are foods and situations beyond the scope of our current packaged foods risk assessment with meals prepared in restaurants, catered meals or home cooked meals, and possibly other larger packaged foods as examples. Additionally, packaged foods with the contamination of multiple accidental, unintended whole kernels of peanut or a packaged product where peanut is indicated as an ingredient would likely contain higher concentrations of peanut than those in our current risk assessment. It is important to note that increasing one's threshold dose for peanut does not allow individuals cosensitized to other foods such as tree nuts to change their avoidance strategies for trace amounts of other offending allergens in packaged foods. Nonetheless, the margin of safety inferred by increasing an individual's threshold dose to 300 mg peanut protein at DBPCFC provides an important protective buffer during daily life and possible exposures to trace amounts of peanut.

One possible limitation of the current study is the use of a threshold value at a single point in time. Some studies have shown that individual thresholds can vary over time.[37-39] Additionally, extrinsic factors such as exercise, sleep deprivation, alcohol, and food matrix during consumption could influence the occurrence of an

allergic reaction.[40] Based on available data, it is known that individual heterogeneity exists as to an increase or decrease in threshold at the repeated DBPCFC, but the average threshold across the population increases or at least remains steady over time.[37] We acknowledge that an individual threshold may vary slightly over time, but the DBPCFC is the gold standard for food allergy diagnosis and primary outcome of food allergen immunotherapy is to measure the degree of desensitization, or the change in the threshold by a food challenge, preferably a DBPCFC.[41] Thus, we have remained consistent with clinical recommendations for our current analysis.

It is important to also discuss the results of this study in a larger European and global context. Earlier efforts have developed a method for combining and comparing consumption data from different countries and results from the Netherlands, France, and Denmark indicate similar consumption patterns of packaged foods across the three countries.[42] Additionally, the EFSA Comprehensive European Food Consumption Database is publicly available and developed for calculation of acute or chronic exposure estimates in EU food risk assessments and includes detailed consumption data from a number of countries including the United Kingdom, Denmark, Finland, Slovenia, Austria, Italy, Hungary, Sweden, Czech Republic, Latvia, Ireland, Belgium, Spain, Greece, Slovakia, France, Netherlands, Cyprus, Poland, Estonia, Bulgaria, Germany, and Romania.[35] On average, adults eating ice cream in different consumption surveys reported a mean daily consumption of 98 g/day across countries with a maximum mean daily consumption of 152 g/day. In a simulation replicating the worst-case ice cream consumption scenario across European countries, individuals reaching a post-immunotherapy individual threshold value of 300 mg peanut protein experienced a predicted 96.3%-99.4% reduction in risk of an allergic reaction due to unintentional presence of peanut. Therefore, it is possible to foresee the protective benefits of peanut immunotherapy demonstrated in the current study applying to the larger European population of peanut-allergic individuals. In comparison, peanut-allergic ice cream consumers who reach a post-immunotherapy individual threshold value of 300 mg peanut protein experience a predicted to a 99.3%->99.9% reduction in risk in the Netherlands or 94.9%-99.5% reduction in risk as previously reported in the United States.[26]

Moreover, the similarities between European and USA average gram consumption estimates detailed earlier for the selected packaged food categories indicate a larger pattern of consumption across Western nations. Interestingly, the maximum reported consumption amounts in the current study were not large enough to cause predicted reactions if an individual achieved a 300 mg peanut protein threshold after immunotherapy in all food categories except ice cream being consumed by adolescents-adults (>99.9% in Table 3), while Baumert et al[26] predicted reactions in all food categories consumed by individuals with a post-immunotherapy threshold of 300 mg peanut protein. However, the observed difference in maximum reported consumption amounts did not significantly alter the outcomes of the two studies and similar risk reduction results were found when statistical distributions were utilized to generate maximum consumption estimates higher than those reported in DNFCS. Furthermore, Kruizinga et al[43] conducted a sensitivity analysis on various inputs for the quantitative risk modeling of allergens in food and found that an increase in the amount of food consumed had a relatively small effect on the estimated number of reactions when compared to other inputs; that is, small variations in consumption would not be expected to produce significantly different results. Thus, it is expected that the protective results of this study would extend to peanut-allergic individuals in other Western countries (ie, Canada, Australia) as well, even if their populations report slightly different maximum values.

We conclude that immunotherapy achieving an eliciting dose of 300 or 1000 mg peanut protein is clinically relevant for the European peanut-allergic population. It is important to note that our risk analysis clearly predicts a protection for peanut-allergic individuals struggling with the uncertainty of the current packaged food (PAL) labeling situation. Benefits of an increased threshold include a clinically relevant reduction in risk due to unintended exposures to traces of peanut protein.

CONFLICT OF INTEREST

This study was conducted in part through an independent research grant from DBV Technologies. B.C. Remington and T. Krone have received money for their institution from the Dutch Ministry of Health, but these funds do not control the design or results of the current study. S. Koppelman has received consultancy fees from DBV Technologies, but these funds do not control the design or results of the current study.

AUTHOR CONTRIBUTION

Dr. B.C. Remington contributed to the overall study design, analyses conducted, interpretation of results, and conclusions drawn. Dr. T. Krone contributed to the design of analytical methods and helped conduct analysis for the study. Dr. S. Koppelman contributed to the overall study design, interpretation of results, and conclusions drawn.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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Supplementary Material

Supplementary Table 1. Food products utilized for cookie exposure estimates as found within the Dutch 2007-2010 National Food Consumption Survey (DNFCS) database and labelled with the common European Food Safety Authority (EFSA) food categories for consumption surveys (FoodEx2).

FoodEx2 classification	Description
A009V	Biscuits (sweet and semi-sweet)
A009X	Biscuits, sweet, plain
A009Y	Butter biscuits
A00AA	Biscuits, sweet, wheat wholemeal
A00AB	Biscuits, oat meal
A00AC	Biscuits, spelt meal
A00AD	Speculaas
A009Z	Biscuits, chocolate
A00AE	Biscuit, filled (with inclusions, filling or coating)
A00CN	Macaroons
A00CP	Meringue
A00CS	Lebkuchen
A00CT	Gingerbread

Supplementary Table 2. Food products utilized for doughnut exposure estimates as found within the Dutch 2007-2010 National Food Consumption Survey (DNFCS) database and labelled with the common European Food Safety Authority (EFSA) food categories for consumption surveys (FoodEx2).

FoodEx2 classification	Description
A00AJ	Beignets
A00BK	Yeast leavened pastry
A00BR	Doughnuts-berliner
A00BT	Brioche

Supplementary Table 3. Food products utilized for croissant exposure estimates as found within the Dutch 2007-2010 National Food Consumption Survey (DNFCS) database and labelled with the common European Food Safety Authority (EFSA) food categories for consumption surveys (FoodEx2).

FoodEx2 classification	Description
A00BM	Croissant
A00BN	Croissant, filled with chocolate
A00BP	Croissant, filled with cream
A00BQ	Croissant, filled with jam

Supplementary Table 4. Food products utilized for salty snack exposure estimates as found within the Dutch 2007-2010 National Food Consumption Survey (DNFCS) database and labelled with the common European Food Safety Authority (EFSA) food categories for consumption surveys (FoodEx2).

FoodEx2 classification	**Description**
A00FB	Other cereal-based snacks
A00FC	Corn chips
A00FD	Tortilla chips
A00FE	Corn curls
A00FG	Sticks, salty
A00FH	Mixed cereal-based snacks

Supplementary Table 5. Food products utilized for ice cream exposure estimates as found within the Dutch 2007-2010 National Food Consumption Survey (DNFCS) database and labelled with the common European Food Safety Authority (EFSA) food categories for consumption surveys (FoodEx2).

FoodEx2 classification	**Description**
A02PZ	Dairy ice creams and similar
A02QA	Ice cream, milk-based
A02QB	Ice cream, milk-imitate based
A02QC	Frozen yoghurt
A04NT	Other ice cream and similar
A036J	Water-based ice creams
A036K	Sorbet

Supplementary Table 6. *Simulated* consumption summary statistics from risk assessments performed in this study. Consumption estimates for the risk assessment simulations closely match the sampled consumptions as reported by the Dutch 2007-2010 National Food Consumption Survey (DNFCS). Two age groups were studied separately, Children (7-11 years) and adolescents-adults (12-69 years).

Cookies	**N**	**Mean (g)**	**Std dev (g)**	**P90 (g)**	**P95 (g)**	**Max (g)**
Child		36.8	21.0	59	72	135
Adolescent-adult		34.7	23.0	59	70	225

Croissants		**Mean (g)**	**Std dev (g)**	**P90 (g)**	**P95 (g)**	**Max (g)**
Child		53.1	23.5	80	100	120
Adolescent-adult		65.2	34.7	120	144	240

Doughnuts		**Mean (g)**	**Std dev (g)**	**P90 (g)**	**P95 (g)**	**Max (g)**
Child		50.9	24.5	70	118	140
Adolescent-adult		74.9	51.7	140	205	285

Ice cream		**Mean (g)**	**Std dev (g)**	**P90 (g)**	**P95 (g)**	**Max (g)**
Child		71.5	29.8	105	122	183
Adolescent-adult		93.5	44.9	150	183	330

Salty snacks		**Mean (g)**	**Std dev (g)**	**P90 (g)**	**P95 (g)**	**Max (g)**
Child		29.4	17.4	59	59	100
Adolescent-adult		40.1	30.5	79	100	175

Supplementary Figure 1. Risk reduction calculations for children and adolescents-adults consuming cookies, croissants, doughnuts, ice cream or salty snacks due to an increase in threshold.

Cookies - Children		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	28.5%	57.9%	84.5%	99.3%	>99.99%	>99.99%
	3		0.0%	41.1%	78.3%	99.0%	>99.99%	>99.99%
	10			0.0%	63.2%	98.4%	>99.99%	>99.99%
	30				0.0%	95.6%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Croissants - Children		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	25.5%	50.8%	75.4%	98.9%	>99.99%	>99.99%
	3		0.0%	33.9%	67.0%	98.5%	>99.99%	>99.99%
	10			0.0%	50.0%	97.7%	>99.99%	>99.99%
	30				0.0%	95.4%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Doughnuts – Children		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	25.4%	50.7%	76.1%	98.5%	>99.99%	>99.99%
	3		0.0%	33.9%	67.9%	98.1%	>99.99%	>99.99%
	10			0.0%	51.5%	97.1%	>99.99%	>99.99%
	30				0.0%	93.9%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Ice Cream – Children		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	24.2%	49.0%	73.2%	97.3%	>99.99%	>99.99%
	3		0.0%	32.7%	64.6%	96.4%	>99.99%	>99.99%
	10			0.0%	47.4%	94.7%	>99.99%	>99.99%
	30				0.0%	90.0%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Salty Snacks – Children		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	31.1%	61.6%	88.9%	>99.99%	>99.99%	>99.99%
	3		0.0%	44.3%	83.9%	>99.99%	>99.99%	>99.99%
	10			0.0%	71.2%	>99.99%	>99.99%	>99.99%
	30				0.0%	>99.99%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Cookies – Adolescents-adults		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	29.1%	59.2%	85.4%	99.6%	>99.99%	>99.99%
	3		0.0%	42.4%	79.4%	99.4%	>99.99%	>99.99%
	10			0.0%	64.3%	98.9%	>99.99%	>99.99%
	30				0.0%	97.0%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

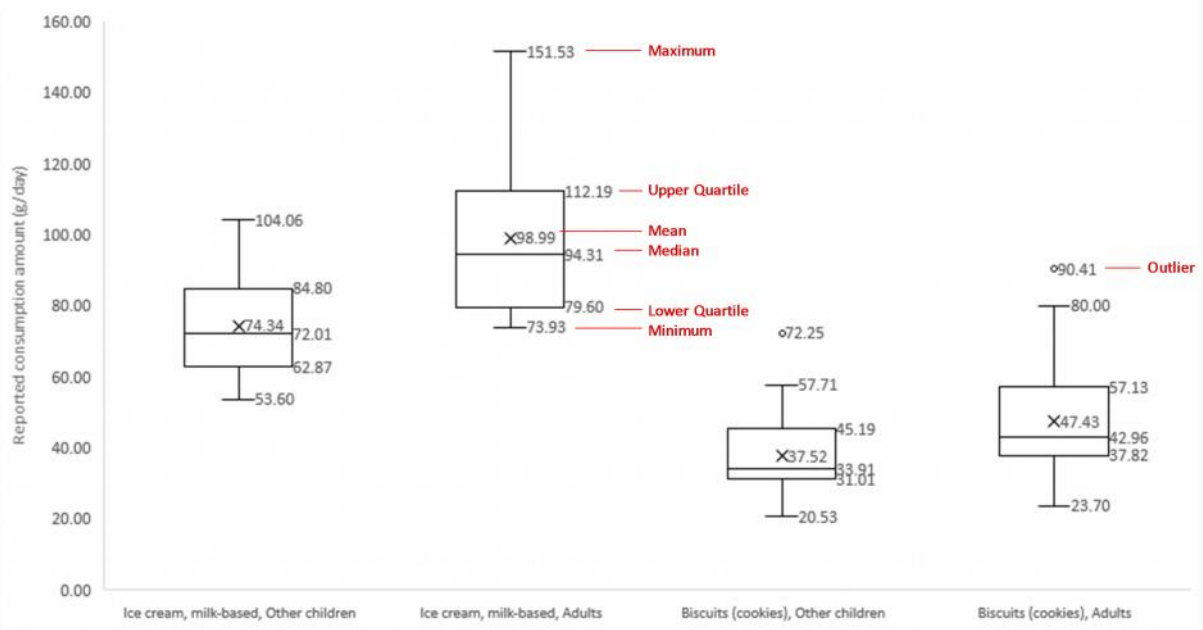
Croissants – Adolescents-adults		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	24.6%	49.1%	73.3%	96.8%	>99.99%	>99.99%
	3		0.0%	32.4%	64.6%	95.8%	>99.99%	>99.99%
	10			0.0%	47.5%	93.7%	>99.99%	>99.99%
	30				0.0%	88.1%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Doughnuts – Adolescents-adults		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	24.1%	48.2%	72.3%	95.1%	>99.99%	>99.99%
	3		0.0%	31.7%	63.5%	93.5%	>99.99%	>99.99%
	10			0.0%	46.5%	90.5%	>99.99%	>99.99%
	30				0.0%	82.3%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Ice Cream – Adolescents-adults		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	23.4%	47.1%	70.6%	93.8%	>99.9%	>99.99%
	3		0.0%	30.9%	61.6%	91.9%	99.9%	>99.99%
	10			0.0%	44.3%	88.3%	99.9%	>99.99%
	30				0.0%	78.9%	99.9%	>99.99%
	100					0.0%	99.3%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Salty Snacks – Adolescents-adults		Threshold Dose – Post Immunotherapy Treatment (mg of peanut protein)						
		1	3	10	30	100	300	1000
Baseline Threshold Dose (mg of peanut protein)	1	0.0%	28.8%	58.0%	84.4%	98.9%	>99.99%	>99.99%
	3		0.0%	41.1%	78.1%	98.4%	>99.99%	>99.99%
	10			0.0%	62.8%	97.3%	>99.99%	>99.99%
	30				0.0%	92.7%	>99.99%	>99.99%
	100					0.0%	>99.99%	>99.99%
	300						0.0%	>99.99%
	1000							0.0%

Supplementary Figure 2. Reported daily mean consumption estimates from 22 countries with children and adults consuming ice cream or cookies in the EFSA Comprehensive European Food Consumption Database. The average gram/day consumption amount at a Foodex L3 description has been reported by EFSA for each individual country from their respective. The mean, median, upper & lower quartiles, as well as the minimum and maximum values of the per country reported average gram/day consumption amounts are detailed here. For instance, adult consumption of the category ice cream has a mean 99g/day (range of 74g/day [Austrian Study on Nutritional Status 2005-06] – 152g/day [The Danish National Dietary survey 2005-2008]).



Data is publicly available and developed for calculation of acute or chronic exposure estimates in EU food risk assessments includes detailed consumption data from a number of countries including the United Kingdom, Denmark, Finland, Slovenia, Austria, Italy, Hungary, Sweden, Czech Republic, Latvia, Ireland, Belgium, Spain, Greece, Slovakia, France, Netherlands, Cyprus, Poland, Estonia, Bulgaria, Germany and Romania (40). It should be noted that the EFSA Comprehensive European Food Consumption Database expresses exposure in gram/day while allergic reactions are acute in nature and occur within a limited time period. It is recommended to use exposure per eating occasion for allergen risk assessments which is expressed as gram/eating occasion in the current study. Despite the small difference in duration of possible exposure, the food categories of cookies and ice cream could easily be matched between the two studies for conservative comparison. Children and adults across European consumption databases reported a mean daily consumption of 38g/day (interquartile range of 31 – 45g/day) and 47g/day (interquartile range of 37 – 57g/day) for cookies in comparison to our respective Dutch estimates of 36.8g/eating occasion and 34.7g/eating occasion. Throughout Europe, children and adults reported a mean daily consumption of 74g/day (interquartile range of 63 – 85g/day) and 99g/day (interquartile range of 80 – 112g/day) for ice cream in comparison to our respective Dutch estimates of 71.5g/eating occasion and 93.5g/eating occasion. It is normal and expected that the reported consumption of grams per day could be slightly higher than grams per eating occasion due to some individuals consuming the same food multiple times in one day. Additionally, Kruizinga et al. (48)

previously conducted a sensitivity analysis on the food allergen probabilistic risk assessment model and demonstrated that an increase in the amount of food consumed did not lead to a similar increase in the number of estimated allergic reactions. Thus from the available data it was concluded that consumption amounts are similar across Europe for the packaged foods in this study.

Supplementary Figure 3. For an added measure of conservatism, an additional quantitative risk assessment was conducted to simulate the worst-case consumption scenario across European countries by utilizing the highest levels of reported daily consumption for ice cream in Europe. The two highest reported European daily consumptions of milk-based ice cream by adults were in Austria (152g/day) and Estonia (151g/day) with both countries reporting a 99th percentile of consumption as 500g/day. As detailed individual data for Austria and Estonia were not available to the authors, data from the adolescents-adults (12-69 years) reporting the consumption of ice cream in the Dutch National Food Consumption Survey were used with an additional a multiplication factor of 160% applied to each eating occasion for a mean consumption of 150g/eating occasion and a maximum eating occasion of 528g, indistinguishable estimates from the maximum reported daily consumptions of ice cream in Europe. The risk reduction calculations due to an increase in threshold are presented below for adolescents-adults consuming the highest reported amounts of ice cream across Europe.

Ice Cream - Adolescents-adults		**Threshold Dose – Post-Immunotherapy Treatment (mg of peanut protein)**						
		1	**3**	**10**	**30**	**100**	**300**	**1000**
Baseline Threshold Dose (mg of peanut protein)	**1**	0.00%	20.60%	42.10%	62.80%	84.20%	99.40%	>99.99%
	3		0.00%	27.10%	53.20%	80.10%	99.30%	>99.99%
	10			0.00%	35.80%	72.70%	99.00%	>99.99%
	30				0.00%	57.60%	98.40%	>99.99%
	100					0.00%	96.30%	>99.99%
	300						0.00%	>99.99%
	1000							0.00%

In European countries with the highest reported levels of ice cream consumption, individuals reaching a post-immunotherapy individual threshold value of 300 mg peanut protein experienced a predicted 96.3 – 99.4% reduction in risk of an allergic reaction due to unintentional presence of peanut, in comparison to a 99.3% – >99.9% in the Netherlands or 94.9 – 99.5% as previously reported in the United States (28).

From the available data in this study, consumption distributions with mean estimates of 29 – 150g/eating occasion and maximums up to 528g per eating occasion have been tested to cover the entire relevant range of reported consumptions across Europe for the five packaged foods of interest (cookies, croissants, doughnuts, ice cream, salty snacks). Thus, we conclude that immunotherapy achieving an eliciting dose of 300 or 1000 mg peanut protein is clinically relevant for the European peanut-allergic population.