

Original Article

Quantitative Assessment of the Safety Benefits Associated with Increasing Clinical Peanut Thresholds Through Immunotherapy

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What is already known about this topic? Immunotherapy for peanut allergy can increase the threshold of peanut protein to which peanut-allergic individuals react.

What does this article add to our knowledge? This article provides a quantitative assessment of the risk reduction of an allergic reaction associated with such increase in threshold.

How does this study impact current management guidelines? This study allows to better estimate the clinical benefit of immunotherapy for peanut allergy and equips health care providers with objective information for the management of peanut-allergic patients who underwent immunotherapy.

BACKGROUND: Peanut immunotherapy studies are conducted with the aim to decrease the sensitivity of patients to peanut exposure with the outcome evaluated by testing the threshold for allergic response in a double-blind placebo-controlled food challenge. The clinical relevance of increasing this threshold is not well characterized.

OBJECTIVE: We aimed to quantify the clinical benefit of an increased threshold for peanut-allergic patients.

METHODS: Quantitative risk assessment was performed by matching modeled exposure to peanut protein with individual threshold levels. Exposure was modeled by pairing US consumption data for various food product categories with potential contamination levels of peanut that have been

demonstrated to be present on occasion in such food products. Cookies, ice cream, doughnuts/snack cakes, and snack chip mixes were considered in the risk assessment.

RESULTS: Increasing the baseline threshold before immunotherapy from 100 mg or less peanut protein to 300 mg peanut protein postimmunotherapy reduces the risk of experiencing an allergic reaction by more than 95% for all 4 food product categories that may contain trace levels of peanut residue. Further increase in the threshold to 1000 mg of peanut protein had an additional quantitative benefit in risk reduction for all patients reacting to 300 mg or less at baseline.

CONCLUSIONS: We conclude that achieving thresholds of 300 mg and 1000 mg of peanut protein by peanut immunotherapy is clinically relevant, and that the risk for peanut-allergic patients who have achieved this increased threshold to experience an allergic reaction is reduced in a clinically meaningful way. © 2017 American Academy of Allergy, Asthma & Immunology (J Allergy Clin Immunol Pract 2017;■:■-■)

Key words: Peanut allergy; Immunotherapy; Risk reduction; Efficacy

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Peanut allergy is a life-threatening, generally persistent food allergy and its prevalence has increased in the last decades to 1% to 2% of children in Western countries.^{1,2} Strict avoidance of peanut consumption and use of rescue medication on occasions of unintentional peanut ingestion are the current ways of managing peanut allergy in the United States³ and Europe.⁴ Because of the wide distribution of peanut as a food ingredient in packaged foods and in restaurant and catering meals, complete avoidance is difficult and peanut-induced anaphylaxis occurs frequently.^{5,6} Allergic reactions can be triggered by minute amounts of peanut protein as demonstrated by several studies that have evaluated individual thresholds and population threshold of peanut-allergic individuals.⁷⁻¹⁰

*Abbreviations used**DBPCFC- double-blind, placebo-controlled food challenge**NHANES- National Health and Nutrition Examination Survey**PAL- precautionary allergen labeling**ppm- parts per million (mg per kilogram of food)*

Packaged food products do on occasion contain unintended allergen residue despite efforts to minimize cross-contact.^{11,12} In these instances, food manufacturers use voluntary precautionary allergen labeling (PAL) such as “May Contain Peanut,” “Processed on Shared Equipment with Peanut,” “Processed in a Facility that Also Processes Peanut,” or similar statements to communicate potential risk to allergic consumers; however, the wide use of such statements has caused some allergic consumers to ignore these advisory statements and consume the product.¹² Several retail surveys have been conducted to ascertain the concentrations of peanut residue, often expressed in parts per million (ppm, which is equal to mg of peanut residue per kg of food product), that may be present in packaged foods bearing PAL.^{13–20} The reported concentration of peanut residue (ppm) can be used to calculate an exposure dose by multiplying by the consumed amount of the product that may contain the peanut residue (as illustrated in Table 1).

Although these retail surveys do present a snapshot in time and varying levels may be present in these same food products that are produced on another day, peanut residue has occasionally been found in packaged food products at concentrations ranging generally from 0.63 to 1000 ppm peanut protein, which could present a risk for peanut-allergic consumers. Increasingly, allergic consumers are ignoring PAL or assigning potential risk to a product on the basis of the type of PAL present on the package label even though past retail surveys have indicated that the type of PAL does not correlate with the probability of the presence of allergen residue or the concentration of this residue.¹² The peanut content of prepackaged products in the US retail market including baked goods, candy/confections, cereal bars, frozen desserts, snack foods, and nutrition bars bearing PAL or no indication of peanut as an ingredient on the package label was surveyed recently, revealing that nutrition bars had the highest concentrations of unintended peanut residue (ie, peanut was not included as an ingredient in the food product formulation but was present because of cross-contact during production).²⁰ In bars surveyed in 2010 that did not contain peanut as an ingredient but that either had PAL regarding the potential presence of peanut ($n = 159$) or no mention of the potential presence of peanut ($n = 49$), the bars with detectable peanut residue ($n = 14$) ranged in concentration from 3.1 to 26,000 ppm peanut or 0.8 to 6500 ppm peanut protein based on an average of 25% protein in peanut as reported by the United States Department of Agriculture National Database for Standard Reference (Release 28),²¹ with a mean of 496 ppm peanut protein and a median of 7.1 ppm peanut protein. It is important to note that nutrition bars bearing a “Unique Label” in this survey included peanut as a minor ingredient but also included a PAL statement for peanut or generically “nuts” that may include peanuts. Although 6500 ppm peanut protein was detected in a nutrition bar sample, the other bars with detectable peanut residue contained significantly lower concentrations of peanut residue (0.78–315 ppm peanut protein; mean, 33.7 ppm; median, 4.4 ppm). An earlier survey reported up to 4000 ppm

peanut (1000 ppm peanut protein) in nutrition bars in the United States.¹⁵ No other published retail surveys have indicated similarly high levels of peanut residue (>1000 ppm peanut protein) in other packaged food products, leading us to believe that the single sample containing 6500 ppm peanut protein may be an isolated event that does not reflect the typical range of peanut residue that may be present in packaged food products bearing PAL statements.

To illustrate what concentration levels expressed in ppm of peanut protein mean, the following example is given. A concentration of 496 ppm of peanut protein in a food product weighing 2 oz (59.1 g) corresponds to $496 \times 1/1,000,000 \times 59.1 = 0.0293$ g or 29.3 mg peanut protein, which, in turn, corresponds to 117 mg of peanut or about 1/10 part of a large-kernel peanut such as Virginia. This example reflects only a selected amount of consumption and peanut protein concentration. An individual exposure dose will change depending on the amount of the food product that is consumed during an eating occasion. Quantitative risk modeling as discussed below is needed to describe exposure doses of peanut protein that peanut-allergic consumers may encounter.

Thus far no therapeutic intervention is available for peanut allergy. Several immunotherapy approaches are being clinically evaluated and show promise in terms of decreased sensitivity to peanut ingestion.^{22,23} The end point for efficacy for such immunotherapy trials (oral,^{24–27} sublingual,^{23,28–30} or epicutaneous^{31–33} immunotherapy) is an increase in an individual’s threshold (eliciting dose) or in the cumulative reactive dose as tested in a double-blind, placebo-controlled food challenge (DBPCFC). To further determine the clinical relevance of reaching a higher threshold through immunotherapy, we have applied quantitative (probabilistic) risk modeling using food consumption data from the 2003–2010 National Health and Nutrition Examination Surveys (NHANES). We have calculated the probability of an allergic reaction for given threshold doses and quantified the protection against accidental exposure to unintended peanut residue that may be present in prepackaged food products upon an increase in threshold provided by immunotherapy.

METHODS

Input parameters for quantitative risk assessment

The quantitative risk assessment model incorporates a number of input variables to predict the allergenic risk associated with the exposure to residual peanut protein in food products.²⁰ The 2 primary input variables that were included in the assessment were the clinical threshold for peanut-allergic individuals and the exposure dose of peanut residue, as specified below.

Clinical threshold for peanut-allergic individuals. The potential decrease in a peanut-allergic individual’s risk to accidental exposure to peanut protein in food products was assessed by a series of individual quantitative risk assessments in which the individual clinical threshold used in the model was held constant at 1, 3, 10, 30, 100, 300, or 1000 mg of peanut protein, reflecting the semi-logarithmic dosage increase recommended for DBPCFC.³⁴ These doses also represent the range of individual threshold doses found for peanut-allergic individuals on graded DBPCFC.⁹ A meta-analysis study summarizing these studies show that the thresholds range from less than 1 mg to several grams of peanut protein, with the majority (82%) of interval-censored individuals (those with defined

TABLE I. Exposure dose calculation

Form of peanut	Concentration		Consumed amount		Dose
Peanut <i>residue</i>	ppm (or mg/kg)	×	kg (or g/1000)	=	mg Peanut <i>residue</i> ↓ × 0.25*
Peanut <i>protein</i>	ppm (or mg/kg)	×	kg (or g/1000)	=	mg Peanut <i>protein</i>

*Peanut kernel contains 25% peanut protein on average.

thresholds based on established no observed adverse effect levels and lowest observed adverse effect levels during oral food challenge) between 1 mg and 1000 mg.^{8,9} A minority of interval-censored individuals (0.5%) will react to doses of less than 1 mg peanut protein, whereas 17.5% will react only to doses of more than 1000 mg peanut protein (corresponding to ~4 large peanut kernels), and it can be questioned whether these peanut-allergic patients are at risk for accidental ingestion of peanut residue that may be present in foods bearing PAL. In our risk modeling study, we therefore focus on thresholds ranging from 1 mg to 1000 mg of peanut protein, using semi-log increments. Holding the clinical threshold value constant for each quantitative assessment allowed us to evaluate the probability of a reaction occurring in an individual with a 1 mg threshold at baseline versus the probability of a reaction occurring in this same individual who has achieved a 300 mg threshold (for example) through successful immunotherapy who may be exposed to various different peanut protein concentrations that may be present in various packaged food products (discussed below).

Consumption data for various product categories. The consumption distribution based on individual consumption patterns recorded in the 2003-2010 NHANES was used to model food product consumption. NHANES is a dietary survey of consumers in the United States that is conducted on 2-year cycles. Consumption data that were collected from the 2003-2010 surveys (4 surveys in total) were used to determine the distribution of consumption (g) of the relevant food product category, excluding products that were described to contain peanuts or peanut butter. Food product categories in the series of quantitative risk assessments included cookies, ice cream, doughnuts/snack cakes, and snack chip mixes (for the product categories and food codes used for exposure dose estimates, see Tables E1-E4 in this article's Online Repository at www.jaci-inpractice.org). These product categories were selected because they fall within the broad food commodity groups that consistently had the highest number of associated Food and Drug Administration Reportable Food Registry entries over the 5-year history of the registry.³⁵ Gendel and Zhu³⁶ further reported that bakery and snack food items accounted for the majority of food allergen-related recalls in the United States. Food products within these categories are commonly consumed in the United States, which allowed for modeling of a wide distribution of reported consumption values. Our risk assessment takes into account the smallest gram quantity of consumption of each product to the largest consumption reported in the data set, so the analysis is quite conservative and reflects typical consumption trends in the US population.

Concentration of peanut protein residue. The potential distribution of peanut protein concentrations that may be found in everyday exposure scenarios due to unintended peanut residue in packaged foods was used by random selection of a peanut protein concentration from a semi-logarithmic distribution of values (1, 3, 10, 30, 100, 300, and 1000 ppm peanut protein). These values were

chosen because they represent a wide distribution of peanut protein concentrations that have been observed in packaged food products bearing PAL statements such as "May Contain Peanut" as mentioned previously in the introductory remarks of this article. Excluding the 1 reported outlier discussed previously,²⁰ we used a concentration of 1000 ppm peanut protein as an upper limit for the potential unintended peanut residue based on Hefle et al¹⁵ and other publications. In our risk assessment, it was assumed that 100% of the food products contained peanut protein residue, with concentrations varying from 1 ppm to 1000 ppm peanut protein. We acknowledge that less than 10% of packaged food products contain detectable levels of peanut protein based on studies previously discussed, so our risk analysis is highly conservative. However, by assuming that all the packaged food products that were evaluated contained peanut residue, we are able to establish statistically a conservative estimate of the probability of a reaction occurring if a peanut-allergic individual was to purchase and consume the product containing peanut residue.

Quantitative risk assessment modeling

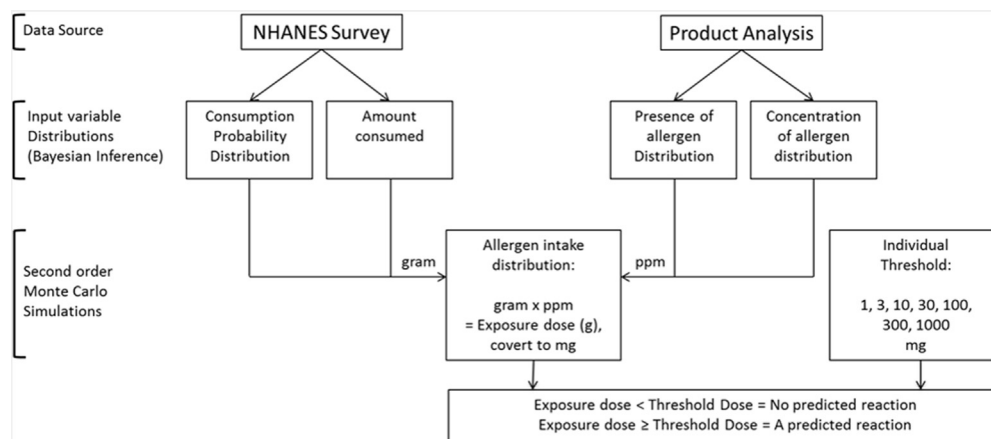
The quantitative (probabilistic) risk assessment was based on the models described by Spanjersberg et al³⁷ and Kruizinga et al,³⁸ modified to incorporate a Bayesian framework to better estimate the SE associated with the risk of allergic reaction.^{20,39} The series of risk assessments reported here all used consumption distributions that were modeled for each food product category, which included a wide range of individual consumption values. The percentage of individuals who would consume the relevant food products on any given eating occasion (based on the NHANES, as summarized in Table II) was also included in our risk analysis. The risk model incorporated a Monte-Carlo simulation for random selection of a peanut residue concentration (1, 3, 10, 30, 100, 300, and 1000 ppm peanut protein) and paired this with a random selection of a consumption value selected from the lognormal consumption distribution generated from the NHANES data for each product category to generate an allergen exposure dose. Multiple iterations of the risk simulation (discussed below) were run to generate an exposure distribution (mg peanut protein). Figure 1 shows the overall approach of the quantitative risk assessment applied in this study.

In each risk assessment simulation, 100,000 randomly selected points from the exposure dose distribution were selected and each exposure dose was compared with the threshold dose (held constant at 1, 3, 10, 30, 100, 300, or 1000 mg peanut protein) to determine whether the risk of an allergic reaction was present; that is, if the exposure dose (mg peanut protein) was greater than or equal to the threshold (mg peanut protein) for each individual simulation, a reaction would be predicted to occur.

This was repeated 50 times for a total of 5,000,000 simulations for each individual risk assessment. The probability of a reaction occurring was presented as the peanut-allergic individual risk (also referred to as peanut-allergic user risk in past publications using quantitative risk assessment models^{17,19,20}) and as the peanut-allergic

TABLE II. US population consumption estimates based on the 2003-2010 US NHANES

Food category	No. of individuals who reported consuming the food (% of total population surveyed)	Single eating occasion consumption estimates (g)				
		Average	90th Percentile	95th Percentile	99th Percentile	Maximum
Snack chip mixes	7,802 (23.6%)	37	64	96	172	380
Cookies	11,297 (34.2%)	32	78	105	178	634
Doughnuts/snack cakes	2,128 (6.44%)	73	128	155	225	768
Ice cream	7,877 (23.9%)	125	240	291	441	1227

**FIGURE 1.** Overall approach of quantitative risk assessment.

population risk. The peanut-allergic individual risk is the most statistically conservative estimate in which it is assumed that all individuals are peanut-allergic and all consume a product that contains peanut residue ranging from 1 to 1000 ppm peanut protein during every eating occasion. We are aware that peanut-allergic individuals within the community are not likely to consume one of the products within the categories that were selected for this risk analysis during every eating occasion based on consumption trends identified from the NHANES. This would further decrease the probability that a reaction would be experienced within the peanut-allergic community during everyday life because potential exposure to peanut residue would not occur if these particular foods were not consumed. To estimate the percentage of reactions within the peanut-allergic community, we have also presented the risk results in terms of the peanut-allergic population risk, which again assumes that all individuals in the population are allergic to peanuts and also includes the percentage of the total surveyed population that reported eating a product within one of these categories during an eating occasion (Table II, column 2). The predicted decrease in risk due to increasing the threshold through immunotherapy is the same for both the peanut-allergic individual and the peanut-allergic population.

RESULTS

For our risk assessment studies, we included the cookie, ice cream, doughnut/snack cake, and snack chip mix product categories, and used consumption data from the NHANES. Table II presents the average quantity of consumption as well as the 90th, 95th, 99th percentile population consumption estimates and the maximum reported consumption quantity for each food product category.

The exposure was modeled using a random selection of a peanut protein concentration from a distribution of values (range, 1-1000 ppm peanut protein) paired with the NHANES consumption data of the 4 product categories. This approach mimics everyday exposure for both the peanut-allergic individual and the overall peanut-allergic population. Our primary focus of this risk assessment modeling is on the peanut-allergic individual risk in which we assume that each individual consumes a product within one of the food categories of interest, each individual is peanut allergic, and each individual has a defined threshold both before and after immunotherapy. This approach allows us to assess the potential risk reduction that is achieved for each peanut-allergic individual. Consumers do not eat foods within these product categories during each eating occasion, so the peanut-allergic individual risk does overestimate the percentage of reactions that would be estimated on any given eating occasion or day and therefore we have also presented the peanut-allergic population risk (Table III). In all cases, we assumed that 100% of the products contained peanut protein. We acknowledge that this would overestimate the risk of reaction that a peanut-allergic individual would experience on any given eating occasion or day because not all products contain trace levels of peanut protein and a peanut-allergic individual would not choose to consume a food from one of these product categories on every eating occasion. Assuming the worst-case scenario of 100% contamination of peanut protein and 100% consumption does however allow us to evaluate the benefit (decrease in predicted risk) that a peanut-allergic individual would experience from an increase in the individual threshold dose after immunotherapy in the event that they were accidentally exposed to trace levels of peanut protein.

TABLE III. Percentage of eating occasions that would result in a predicted allergic reaction

Product category*	Risk category†	Peanut-allergic individual's threshold value (%)						
		1 mg	3 mg	10 mg	30 mg	100 mg	300 mg	1000 mg
Snack chip mixes	Peanut-allergic individual	45.8	32.3	17.6	5.6	0.5	0.009	NR
	Peanut-allergic population	10.8	7.6	4.2	1.3	0.1	0.002	NR
Cookies	Peanut-allergic individual	44.5	31.2	16.2	5.5	0.4	0.012	NR
	Peanut-allergic population	15.3	10.7	5.6	1.9	0.1	0.004	NR
Doughnuts/snack cakes	Peanut-allergic individual	56.0	42.4	27.5	14.0	2.2	0.027	NR
	Peanut-allergic population	3.6	2.7	1.8	0.9	0.1	0.002	NR
Ice cream	Peanut-allergic individual	60.7	46.9	32.3	19.0	5.8	0.295	0.0040
	Peanut-allergic population	14.5	11.2	7.7	4.5	1.4	0.070	0.0010

NR, No reaction predicted.

*Food products were assumed to contain peanut residue. The quantitative risk assessment model randomly selected a concentration of peanut (1, 3, 10, 30, 100, 300, or 1000 ppm peanut protein) during each iteration of the analysis.

†Peanut-allergic individual risk assumes that all individuals in the population are peanut-allergic and all eat a food product within the selected categories during every eating occasion. This is the most statistically conservative approach to the risk analysis. Peanut-allergic population risk assumes that all individuals in the population are allergic to peanuts but not all individuals will consume one of the products during every eating occasion. The percentage of eating occasions used in this risk assessment is based on the NHANES and presented in column 2 of [Table II](#).

To predict an allergic reaction, the modeled exposure is compared with a range of thresholds from 1 mg to 1000 mg of peanut protein, using semi-log increments as discussed previously. [Table III](#) presents the percentage of eating occasions that would result in a predicted allergic reaction as a function of the peanut-allergic individual's threshold (individual risk) as well as risk for the peanut-allergic population that takes into account the percentage of the population that reported consuming a food within the product category on any given eating occasion. In several cases, no allergic reactions were predicted because the maximum consumption amount in our consumption distribution limits the exposure to values below the highest threshold, even in the case that a peanut protein concentration of 1000 ppm was present. For example, an individual with a 1000 mg peanut protein threshold would need to consume 1000 g or more of a cookie product containing 1000 ppm peanut protein to exceed their threshold dose (1000 ppm of 1000 g equals 1000 mg), which is not likely to occur on the basis of NHANES data. For ice cream, the consumption amounts are higher than for cookies on a population basis ([Table II](#)) and the risk modeling shows that reactions are predicted in peanut-allergic individuals with the higher threshold of 1000 mg, although this percentage is very low ([Table III](#)). The maximum consumption of doughnuts/snack cakes and snack chip mixes is comparable to that of cookies; thus, a reaction in peanut-allergic individuals with a threshold of 1000 mg is not predicted ([Table III](#)). Similar to differences in maximum consumption between the product categories, differences in average consumption are noted as well. Interestingly, the average consumption of doughnuts/snack cakes is more than 2-fold higher than the average consumption of cookies, whereas the maximum consumption is about the same. Another factor playing a role in the prediction of an allergic reaction is the number of individuals who consume a food within a certain product category. Although this is about 1 out of 3 to 4 for cookies, ice cream, and snack chip mixes, only 1 out of 15 individuals report consumption of doughnuts/snack cakes ([Table II](#)). This low frequency of consumption leads to a lower incidence of predicted reaction for doughnuts/snack cakes in the peanut-allergic population ([Table III](#)), even while the average consumption is higher than for cookies and snack chip mixes ([Table II](#)).

Using these percentages of predicted allergic reactions as a function of the peanut-allergic individual's threshold, the decrease in the risk of having an allergic reaction as a function of an increase in threshold can be calculated as explained using the following example for cookies. An individual with a baseline threshold of 30 mg peanut protein who increases the threshold to 300 mg peanut protein after immunotherapy decreases the percentage of a predicted allergic reaction from 1.9% to 0.004% (Peanut-Allergic Individual Risk, [Table III](#)), corresponding to a decrease in risk of $1 - (0.004/1.9) = 0.998$, or 99.8%. This decrease in risk is shown in [Figure 2, A to D](#), for all 4 food product categories. Regardless of the baseline threshold, individuals who reach a threshold after immunotherapy of 300 mg or more of peanut protein show a high reduction in risk of experiencing an allergic reaction (94.9%–99.9% across the different food product categories). For the cookies, doughnut/snack cakes, and snack chip mixes, reaching a post-immunotherapy threshold of 300 mg peanut protein provides optimal reduction in the risk of experiencing an allergic reaction to trace concentrations of peanut residue that may be present occasionally in food products. For ice cream, some additional benefit is obtained when a threshold of 1000 mg peanut protein is achieved after immunotherapy; however, this additional benefit is limited ([Figure 2](#)).

Another way to look at the data is to determine the fold reduction in risk of an allergic reaction. [Figure 3, A](#), shows the fold reduction in risk as a function of baseline threshold for peanut-allergic individuals who reach the 300 mg threshold after immunotherapy. Individuals with low baseline thresholds show the largest fold reduction in risk, yet individuals with a baseline threshold of 100 mg peanut protein also benefit substantially by reaching the 300 mg threshold. The fold reduction in risk when reaching a 300 mg threshold after immunotherapy is lower for ice cream than for the other food product categories due to the higher consumption estimates for ice cream (both when the average and maximum consumption is considered; [Table II](#)). However, peanut-allergic individuals who consume large quantities of a food product such as ice cream that may contain peanut residue would have an additional benefit of further risk reduction from achieving an end-point threshold of 1000 mg after immunotherapy. Based on the maximum consumption

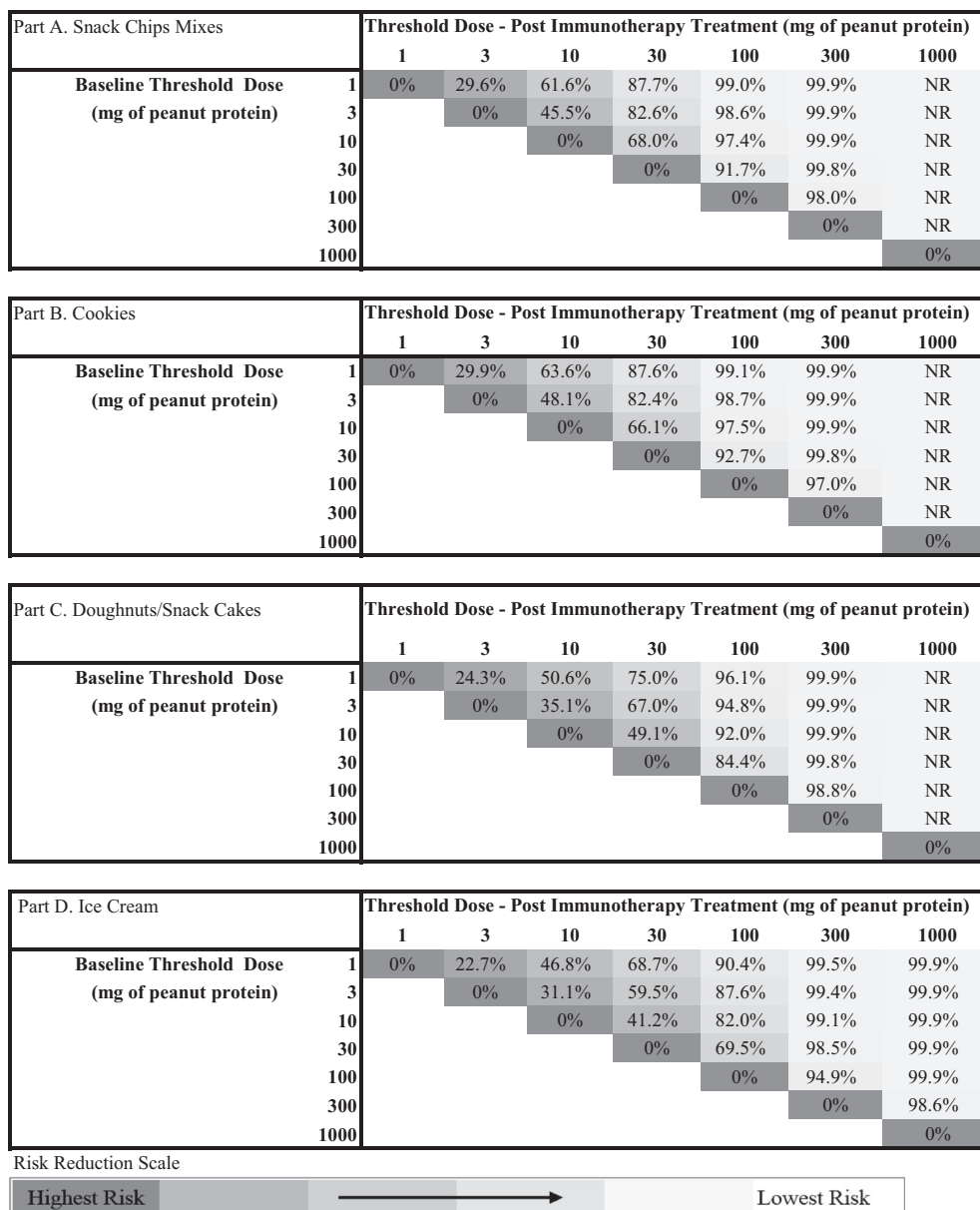


FIGURE 2. Decrease in risk of reaction on consumption of various food products as a function of a change in threshold. *NR*, No predicted reaction.

levels and the assumed contamination levels, the exposure to peanut protein in the case of ice cream exceeds 1000 mg whereas this is not the case for the other food product categories where the combination of the quantity consumed and the highest level of peanut residue do not reach an exposure dose of 1000 mg of peanut protein. Figure 3, B, shows for ice cream that reaching a threshold of 1000 mg provides an additional risk reduction of 70-fold on top of the risk reduction achieved by reaching a threshold of 300 mg, regardless of the baseline threshold.

DISCUSSION

The current management of peanut allergy is to strictly avoid peanut, and to treat symptoms with rescue medication such as

epinephrine when peanut is inadvertently ingested. Several immunotherapy approaches are in clinical development aiming to induce tolerance or to desensitize peanut-allergic patients. Efficacy of such immunotherapy is assessed by determining the individual's threshold for peanut protein by DBPCFC, before and after immunotherapy. Although a clear increase in threshold is observed after immunotherapy in those who respond to treatment, the clinical relevance of such threshold is not evident. The main motivation of peanut-allergic patients to participate in an immunotherapy study is to increase their threshold such that they are protected against anaphylaxis caused by trace amounts of peanut due to accidental exposure, rather than to be able to eat peanut or food products that contain peanut as ingredient.⁴⁰ For the first time, the level of protection provided by peanut

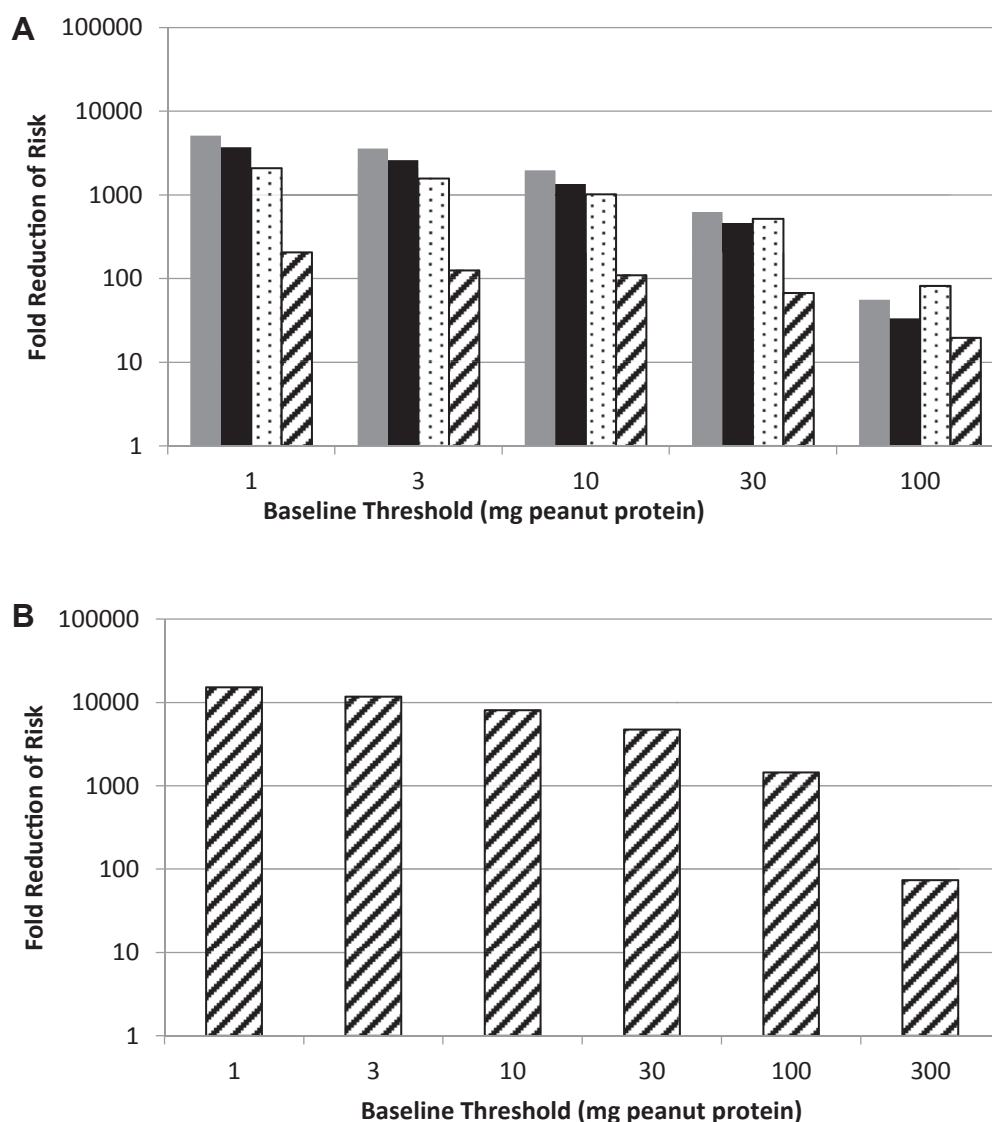


FIGURE 3. Fold reduction in risk for peanut-allergic individuals on increasing the threshold through immunotherapy. **A**, Risk reduction when a threshold of 300 mg peanut protein is reached after immunotherapy. **B**, Risk reduction when a threshold of 1000 mg peanut protein is reached after immunotherapy. Food product categories indicated by gray bars: snack chips mixes; black bars: cookies; dotted bars: doughnuts/snack cakes; dashed bars: ice cream. Note: Panel B for reaching a threshold of 1000 mg is relevant only for ice cream because for the other food product categories no reactions are predicted for individuals who have a threshold of 1000 mg due to the lower consumption quantities involved.

immunotherapy against allergic reactions to food products that contain trace amounts of peanut was demonstrated. The level of protection is based on quantitative risk assessment and comparing food challenge thresholds before and after immunotherapy.

A limitation of this approach is that the repeatability of threshold determination is not well characterized. Therefore, some variability can be expected on an individual basis. A limited number of studies have evaluated the variability of a peanut-allergic individual's threshold in the placebo arm of the immunotherapy trials.^{29,41,42} Based on the limited number of individuals evaluated in these studies, it appears that the threshold can vary over time by approximately 10-fold in the overall population on average with both increases and decreases

in the individual thresholds reported. We acknowledge that a limitation of our assessment is that it evaluates the efficacy of immunotherapy on the basis of a static threshold at a single point in time and that some unknown degree of individual variation in the threshold may occur; however, the Food and Drug Administration has approved the use of DBPCFC as a technique to determine the degree of desensitization that is achieved by immunotherapy. We have chosen to stay consistent with this recommendation in the analysis presented here.⁴³

Highly sensitive peanut-allergic individuals who have a baseline threshold dose of 1, 3, or 10 mg peanut protein before initiation of immunotherapy who could successfully increase their threshold dose to 300 mg of peanut protein would decrease their risk of an allergic reaction over a 100-fold or better after

consumption of a peanut-contaminated food product containing up to 1000 ppm peanut protein. Therefore, reaching a threshold dose of 300 mg of peanut protein, corresponding to the consumption of a large-kernel snack peanut such as Virginia (U.S. Department of Agriculture Grades and Standards) would be a very important milestone in the immunotherapy treatment because this risk simulation demonstrates that these peanut-allergic individuals would tolerate trace levels of unintended peanut protein that may occasionally be found in packaged food products. Although adopting a harmonized risk-based approach such as the Allergen Bureau of Australia and New Zealand's Voluntary Incidental Trace Allergen Labeling program⁴⁴ would provide the most transparent approach for the use of PAL, currently, PAL is allowed on a voluntary basis throughout the world¹² and several studies have demonstrated that a wide range of concentrations of allergen residues can exist in packaged food products as discussed previously. Given the uncertainty associated with the current labeling situation, it is noteworthy that our risk analysis would predict a substantial benefit to individuals who successfully complete food allergen immunotherapy.

An individual threshold dose of 300 mg of peanut protein of course does not mean that peanut-allergic individuals can become cavalier with their peanut avoidance diet because there are food products beyond the packaged food products included in our risk assessment to which peanut-allergic patients are potentially exposed, such as meals at home, restaurants, or catering, that could contain higher concentrations of peanut residue on occasion than those examined in our assessment or where peanut is included as an ingredient in the product formulation. In addition, those peanut-allergic individuals who may be cosensitized to other foods such as tree nuts would need to remain diligent in avoidance of foods that may contain traces of other offending allergens. Nevertheless, increasing one's threshold dose to 300 mg peanut protein during immunotherapy, as measured through DBPCFCs, provides an important margin of safety to protect peanut-allergic individuals from the occasional trace levels of peanut that they may encounter during daily life. The relevance of reaching a threshold of 1000 mg peanut protein through immunotherapy in products that are consumed in larger quantities during a single eating occasion is illustrated by the ice cream product category where an additional 70-fold reduction in the risk of a reaction occurring was observed on increasing the threshold from 300 mg to 1000 mg peanut protein.

We conclude that increasing the threshold for eliciting an allergic reaction from 100 mg or less to 300 mg peanut protein or more, and from 300 mg or less to 1000 mg peanut protein or more are clinically relevant objectives for peanut immunotherapy. The risk for peanut-allergic patients who have successfully increased their threshold to 300 mg peanut protein by immunotherapy to experience an allergic reaction is reduced in a clinically meaningful way.

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ONLINE REPOSITORY

TABLE E1. Cookie product categories from the 2003-2010 NHANES that were included in the quantitative risk assessments

USDA food code	Cookie food code description
53201000	Cookie, not specific to cookie type
53202000	Cookie, almond
53203000	Cookie, applesauce
53203050	Cookie, fruit, baby
53203100	Cookie, baby
53203500	Cookie, biscotti (Italian sugar cookie)
53204000	Cookie, brownie, not specific as to icing
53204010	Cookie, brownie, without icing
53204100	Cookie, brownie, with icing
53204500	Cookie, brownie, with cream cheese filling, without icing
53204800	Cookie, brownie, diet, not specific as to icing
53204830	Cookie, brownie, low fat, with icing
53204840	Cookie, brownie, low fat, without icing
53204850	Cookie, brownie, fat-free, cholesterol free, with icing
53204860	Cookie, brownie, fat-free, without icing
53205250	Cookie, butterscotch, brownie
53205500	Cookie, butterscotch chip
53205600	Cookie, caramel coated, with nuts
53206000	Cookie, chocolate chip
53206010	Cookie, chocolate chip, with raisins
53206020	Cookie, chocolate chip, made from home recipe or purchased at a bakery
53206030	Cookie, chocolate chip, reduced fat
53206050	Cookie, rich, chocolate chip, with chocolate filling
53206100	Cookie, chocolate chip sandwich
53206500	Cookie, chocolate, made with rice cereal
53206550	Cookie, chocolate, made with oatmeal and coconut (no-bake)
53207000	Cookie, chocolate fudge, with/without nuts
53207050	Cookie, chocolate, with chocolate filling or coating, fat-free
53208000	Cookie, chocolate-covered marshmallow
53208200	Cookie, marshmallow pie, chocolate-covered
53209000	Cookie, chocolate, chocolate sandwich or chocolate-coated or striped
53209010	Cookie, chocolate-covered, sugar wafer, creme- or caramel-filled
53209020	Cookie, chocolate sandwich, reduced fat
53209050	Cookie, chocolate-covered, chocolate sandwich
53209100	Cookie, chocolate, sandwich, with extra filling
53209500	Cookie, chocolate and vanilla sandwich
53210000	Cookie, chocolate wafer
53210900	Cookie, graham cracker sandwich with chocolate and marshmallow filling
53210910	Cookie, graham cracker with marshmallow
53211000	Cookie bar, with chocolate, nuts, and graham crackers
53215500	Cookie, coconut
53216000	Cookie, coconut and nut

(continued)

TABLE E1. (Continued)

USDA food code	Cookie food code description
53220000	Cookie, fruit-filled bar
53220010	Cookie, fruit-filled bar, fat-free
53220020	Cookie, date bar
53220030	Cookie, fig bar
53220040	Cookie, fig bar, fat-free
53222010	Cookie, fortune
53222020	Cookie, cone shell, ice cream type, wafer or cake
53222100	Cookie, cone shell, ice cream type, brown sugar
53223000	Cookie, gingersnaps
53223100	Cookie, granola
53224000	Cookie, ladyfinger
53224250	Cookie, lemon bar
53225000	Cookie, macaroon, coconut-meringue type, no flour
53226000	Cookie, marshmallow, with coconut
53226500	Cookie, marshmallow, with rice cereal (no-bake)
53226550	Cookie, marshmallow, with rice cereal and chocolate chips
53227000	Cookie, marshmallow pies, nonchocolate coating
53228000	Cookie, meringue
53230000	Cookie, molasses
53231000	Cookie, Lebkuchen
53231400	Cookie, multigrain, high fiber
53233000	Cookie, oatmeal
53233010	Cookie, oatmeal, with raisins
53233020	Cookie, oatmeal, with fruit filling
53233030	Cookie, oatmeal, fat-free, with raisins
53233040	Cookie, oatmeal, reduced fat, with raisins
53233050	Cookie, oatmeal sandwich, with creme filling
53233060	Cookie, oatmeal, with chocolate chips
53233500	Cookie, oat bran
53236000	Cookie, pizzelle (Italian style wafer)
53236100	Cookie, pumpkin
53237000	Cookie, raisin
53237010	Cookie, raisin sandwich, cream-filled
53237500	Cookie, rum ball (no-bake)
53238000	Cookie, sandwich-type, not chocolate or vanilla
53239000	Cookie, shortbread
53239010	Cookie, shortbread, reduced fat
53239050	Cookie, shortbread, with chocolate filling
53241500	Cookie, butter or sugar cookie
53241600	Cookie, butter or sugar cookie, with fruit and/or nuts
53242000	Cookie, sugar wafer
53242250	Cookie, teething, baby food
53242500	Cookie, toffee bar
53243000	Cookie, vanilla sandwich
53243050	Cookie, vanilla sandwich, reduced fat
53243100	Cookie, rich, all chocolate, with chocolate filling or chocolate chips
53244010	Cookie, butter or sugar, with chocolate icing or filling
53244020	Cookie, butter or sugar, with icing or filling other than chocolate
53245000	Cookie, vanilla waffle creme
53246000	Cookie, tea, Japanese

(continued)

TABLE E1. *(Continued)*

USDA food code	Cookie food code description
53247000	Cookie, vanilla wafer
53247050	Cookie, vanilla wafer, reduced fat
53247500	Cookie, vanilla with caramel, coconut, and chocolate coating
53251100	Cookie, rugelach
53260030	Cookie, dietetic, chocolate chip
53260150	Cookie, lemon wafer, low fat
53260200	Cookie, dietetic, oatmeal with raisins
53260300	Cookie, dietetic, sandwich-type
53260400	Cookie, dietetic, sugar or plain
53270100	Cookies, Puerto Rican (Mantecaditos polvorones)

USDA, United States Department of Agriculture.

TABLE E2. Ice cream product categories from the 2003-2010 NHANES that were included in the quantitative risk assessments

USDA food code	Ice cream food code description
13110000	Ice cream, not specific to type of ice cream
13110100	Ice cream, regular, flavors other than chocolate
13110110	Ice cream, regular, chocolate
13110120	Ice cream, rich, flavors other than chocolate
13110130	Ice cream, rich, chocolate
13110200	Ice cream, soft serve, flavors other than chocolate
13110210	Ice cream, soft serve, chocolate
13110220	Ice cream, soft serve, not specific as to flavor
13110320	Ice cream, no sugar added, flavors other than chocolate
13110330	Ice cream, no sugar added, chocolate
13120050	Ice cream bar or stick, not chocolate-covered or cake covered
13120100	Ice cream bar or stick, chocolate-covered
13120110	Ice cream bar or stick, chocolate or caramel covered, with nuts
13120120	Ice cream bar or stick, rich chocolate ice cream, thick chocolate covering
13120121	Ice cream bar or stick, rich ice cream, thick chocolate covering
13120130	Ice cream bar or stick, rich ice cream, chocolate-covered, with nuts
13120140	Ice cream bar or stick, chocolate ice cream, chocolate-covered
13120300	Ice cream bar, cake covered
13120400	Ice cream bar or stick with fruit
13120500	Ice cream sandwich
13120550	Ice cream cookie sandwich
13120700	Ice cream cone with nuts, flavors other than chocolate
13120710	Ice cream cone, chocolate-covered, with nuts, flavors other than chocolate
13120720	Ice cream cone, chocolate covered or dipped, flavors other than chocolate
13120730	Ice cream cone, no topping, flavors other than chocolate
13120740	Ice cream cone, no topping, not specific as to flavor
13120750	Ice cream cone with nuts, chocolate ice cream
13120760	Ice cream cone, chocolate covered or dipped, chocolate ice cream
13120770	Ice cream cone, no topping, chocolate ice cream
13120790	Ice cream sundae cone
13120800	Ice cream soda, flavors other than chocolate
13121000	Ice cream sundae, not specific as to topping, with whipped cream
13121100	Ice cream sundae, fruit topping, with whipped cream
13121300	Ice cream sundae, chocolate or fudge topping, with whipped cream
13121400	Ice cream sundae, not fruit or chocolate topping, with whipped cream
13122100	Ice cream pie, no crust
13122500	Ice cream pie, with cookie crust, fudge topping, and whipped cream
13126000	Ice cream, fried
13130100	Light ice cream, not specific as to flavor (formerly ice milk)
13130300	Light ice cream, flavors other than chocolate (formerly ice milk)

(continued)

TABLE E2. (Continued)

USDA food code	Ice cream food code description
13130310	Light ice cream, chocolate (formerly ice milk)
13130320	Light ice cream, no sugar added, not specific as to flavor
13130330	Light ice cream, no sugar added, flavors other than chocolate
13130340	Light ice cream, no sugar added, chocolate
13130590	Light ice cream, soft serve, not specific as to flavor (formerly ice milk)
13130600	Light ice cream, soft serve, flavors other than chocolate (formerly ice milk)
13130610	Light ice cream, soft serve, chocolate (formerly ice milk)
13130620	Light ice cream, soft serve cone, flavors other than chocolate (formerly ice milk)
13130630	Light ice cream, soft serve cone, chocolate (formerly ice milk)
13130640	Light ice cream, soft serve cone, not specific as to flavor (formerly ice milk)
13130700	Light ice cream, soft serve, blended with candy or cookies
13135000	Ice cream sandwich, made with light ice cream, flavors other than chocolate
13135010	Ice cream sandwich, made with light chocolate ice cream
13136000	Ice cream sandwich, made with light, no sugar added ice cream
13140100	Light ice cream, bar or stick, chocolate-coated (formerly ice milk)
13140110	Light ice cream, bar or stick, chocolate-covered, with nuts (formerly ice milk)
13140500	Light ice cream, cone, flavors other than chocolate (formerly ice milk)
13140550	Light ice cream, cone, chocolate (formerly ice milk)
13140650	Light ice cream, sundae, soft serve, not fruit or chocolate topping, with whipped cream (formerly ice milk)
13140660	Light ice cream, sundae, soft serve, chocolate or fudge topping (without whipped cream) (formerly ice milk)
13140670	Light ice cream, sundae, soft serve, fruit topping (without whipped cream) (formerly ice milk)
13140680	Light ice cream, sundae, soft serve, not fruit or chocolate topping (without whipped cream) (formerly ice milk)
13140700	Light ice cream, creamsicle or dreamsicle (formerly ice milk)
13140900	Light ice cream, fudgesicle (formerly ice milk)
13160150	Fat-free ice cream, no sugar added, chocolate
13160160	Fat-free ice cream, no sugar added, flavors other than chocolate
13160400	Fat-free ice cream, flavors other than chocolate
13160410	Fat-free ice cream, chocolate
13161630	Light ice cream, bar or stick, with low-calorie sweetener, chocolate-coated (formerly ice milk)
53112000	Cake, ice cream and cake roll, chocolate
53112100	Cake, ice cream and cake roll, not chocolate
53222020	Cookie, cone shell, ice cream type, wafer or cake
53222100	Cookie, cone shell, ice cream type, brown sugar

USDA, United States Department of Agriculture.

TABLE E3. Doughnuts/snack cake product categories from the 2003-2010 NHANES that were included in the quantitative risk assessments

USDA food code	Doughnut/snack cake food code description
53520000	Doughnut, not specific as to cake or yeast
53520110	Doughnut, cake type
53520120	Doughnut, chocolate, cake type
53520140	Doughnut, cake type, chocolate-covered
53520160	Doughnut, chocolate, cake type, with chocolate icing
53521100	Doughnut, chocolate, raised or yeast, with chocolate icing
53521110	Doughnut, raised or yeast
53521120	Doughnut, chocolate, raised or yeast
53521130	Doughnut, raised or yeast, chocolate-covered
53521140	Doughnut, jelly
53521210	Doughnut, custard-filled
53521220	Doughnut, chocolate cream-filled
53521230	Doughnut, custard-filled, with icing
53521250	Doughnut, wheat
53521300	Doughnut, wheat, chocolate-covered

USDA, United States Department of Agriculture.

TABLE E4. Snack chip mix product categories from the 2003-2010 NHANES that were included in the quantitative risk assessments

USDA food code	Doughnut/snack cake food code description
54401010	Salty snacks, corn or cornmeal base, nuts or nuggets, toasted
54401020	Salty snacks, corn or cornmeal base, corn chips, corn-cheese chips
54401050	Salty snacks, corn or cornmeal base, corn puffs and twists; corn-cheese puffs and twists
54401080	Salty snacks, corn or cornmeal base, tortilla chips
54401090	Salty snacks, corn or cornmeal base, corn chips, corn-cheese chips, unsalted
54401100	Salty snacks, corn or cornmeal base, tortilla chips, light (baked with less oil)
54401120	Salty snacks, corn or cornmeal base, tortilla chips, fat-free, made with Olean
54401150	Salty snacks, corn or cornmeal base, tortilla chips, low fat, baked without fat
54401170	Salty snacks, corn or cornmeal base, tortilla chips, low fat, baked without fat, unsalted
54401210	Salty snacks, corn-based puffs and twists, cheese puffs and twists, low fat
54402080	Salty snacks, corn or cornmeal base, tortilla chips, unsalted
54402200	Salty snack mixture, mostly corn or cornmeal based, with pretzels, without nuts
54402500	Salty snacks, wheat- and corn-based chips
54402600	Salty snacks, multigrain, chips

USDA, United States Department of Agriculture.