



Assessing food allergy risks from residual peanut protein in highly refined vegetable oil



W. Marty Blom^{a,*}, Astrid G. Kruizinga^a, Carina M. Rubingh^a, Ben C. Remington^a, René W.R. Crevel^b, Geert F. Houben^a

^a The Netherlands Organisation for Applied Scientific Research TNO, Zeist, The Netherlands

^b Safety and Environmental Assurance Centre (SEAC), Unilever, Colworth Science Park, Sharnbrook, Bedford, United Kingdom

ARTICLE INFO

Article history:

Received 28 March 2017

Received in revised form

19 May 2017

Accepted 30 May 2017

Available online 31 May 2017

Keywords:

Allergen risk assessment

Food allergy

Precautionary allergen labeling

Refined peanut oil

Refined vegetable oils

Unintended peanut protein

ABSTRACT

Refined vegetable oils including refined peanut oil are widely used in foods. Due to shared production processes, refined non-peanut vegetable oils can contain residual peanut proteins. We estimated the predicted number of allergic reactions to residual peanut proteins using probabilistic risk assessment applied to several scenarios involving food products made with vegetable oils. Variables considered were: a) the estimated production scale of refined peanut oil, b) estimated cross-contact between refined vegetable oils during production, c) the proportion of fat in representative food products and d) the peanut protein concentration in refined peanut oil.

For all products examined the predicted risk of objective allergic reactions in peanut-allergic users of the food products was extremely low. The number of predicted reactions ranged depending on the model from a high of 3 per 1000 eating occasions (Weibull) to no reactions (LogNormal). Significantly, all reactions were predicted for allergen intakes well below the amounts reported for the most sensitive individual described in the clinical literature.

We conclude that the health risk from cross-contact between vegetable oils and refined peanut oil is negligible. None of the food products would warrant precautionary labelling for peanut according to the VITAL[®] programme of the Allergen Bureau.

© 2017 Elsevier Ltd. All rights reserved.

1. Introduction

Highly refined peanut oil is considered to pose a risk to people with peanut allergy (EFSA, 2004, 2007). Although that risk has not been characterised, controlled clinical challenges suggest that it is negligible (Hourihane et al., 1997).

Refined vegetable oils may be produced on the same equipment and therefore cross-contact between non-peanut refined vegetable oils and refined peanut oil can occur. Since refined peanut oil contains small amounts of peanut proteins (Crevel et al., 2000; Ramazzotti et al., 2008), refined non-peanut vegetable oils and food products produced with these can unintentionally contain very small levels of peanut protein residues. Evidence exists for the allergenicity of peanut oil (various grades of refinement) based on

the response of peanut-allergic individuals in skin prick testing and is probably due to low levels of biologically active peanut proteins remaining in the oil fraction (Moneret-Vautrin et al., 1998; Olszewski et al., 1998). The study of Hourihane et al. 1997 tested crude peanut oil and refined peanut oil in 62 peanut-allergic patients in a double blind placebo controlled food challenge. None of the subjects reacted to the refined peanut oil, but six reacted with mostly subjective reactions to crude oil. While the dose of peanut oil administered in the food challenge was reported, the peanut protein content of the refined oil was not, and thus the dose of peanut proteins administered is not known. Further, it is not known if these patients were representative of the total peanut-allergic population, as subsequent open challenge with peanut showed only mild reactions.

Recently, a substantial quantity of high quality clinical threshold dose data (n = 750) on objective allergic reactions to peanut protein of the peanut-allergic population was collected and used for threshold dose distribution analyses which informed among others the scientific review of the VITAL[®] scheme (Voluntary Incidental

* Corresponding author. The Netherlands Organisation for Applied Scientific Research TNO, Department Risk Analysis of Products in Development (RAPID), Utrechtseweg 48, 3704 HE, Zeist, The Netherlands.

E-mail address: marty.blom@tno.nl (W.M. Blom).

Abbreviations

LOAEL	lowest observed adverse effect level
N/RBD	neutralised refined bleached and deodorised
NL	Netherlands
NOAEL	no observed adverse effect level
UK	United Kingdom
VITAL®	Voluntary Incidental Trace Allergen Labelling

Trace Allergen Labelling) (Allen et al., 2014; Taylor et al., 2014). Most of the studies on which the data set was based, did not exclude participants with a history of severe reactions and/or anaphylaxis (Taylor et al., 2015). Allergen risk assessment using probabilistic techniques enables quantitative estimation of the probability of an allergic reaction after the consumption of a food product that contains an allergen (Spanjersberg et al., 2007; Crevel et al., 2007; Rimbaud et al., 2010; Remington et al., 2013, 2015). In this paper, we assess the predicted percentage of objective allergic reactions associated with residual peanut protein in refined non-peanut vegetable oil used as an ingredient in consumer food products. By designing several scenarios, varying relevant factors, such as the percentage of cross-contact, concentrations of contaminated vegetable oil and proportion of contaminated products, the probabilistic allergen risk assessment approach provides insight into how these factors affect the possible health risk for the peanut allergic population.

2. Materials and methods

2.1. Data

2.1.1. Concentration of peanut protein in refined peanut oil

Samples of highly refined neutralised, bleached and deodorised (N/RBD) food-grade peanut oil from commercial batches were obtained by FEDIOL, the European Vegetable Oil and Proteinmeal Association, from member companies across Europe. All oils had been produced in accordance with the FEDIOL Code of Practice for oil refining (<http://www.fediol.eu/data/d0234.pdf>) and were analysed for peanut protein content by the Institute of Food Research (Norwich) (IFR) using the method described by Rigby et al. (2011). The measured peanut protein concentration in refined peanut oil was 0.69 ± 0.3 mg peanut protein/kg (average $\pm$ sd) and based on 22 samples in which the concentration ranged from 0.070 to 1.756 mg/kg (IFR, personal commun.). It is important to note that these samples are representative of the major oil producers, but analysis results obtained would not necessarily translate to the outputs of all refiners, unless they were complying with the FEDIOL Code of Practice.

2.1.2. Consumption of food products

Food consumption data for several food products were derived from the National Food Consumption Survey 2003 of the Netherlands (NL) (Hulshof et al., 2004) in adults aged 19 to 30 years, and the National Diet and Nutrition Survey in the United Kingdom (UK), carried out between July 2000 and June 2001. This survey was held among adults aged 19 to 64 years (Office for National Statistics, Food Standards Agency, 2005).

The consumption distribution of food products as determined by those surveys was used. Products were selected for their relatively high contribution to fat consumption in the population, and included biscuits, margarine, ice cream and fried food (see Table 1).

Table 1

Intake of food products selected for study.

description	Country ^a	% fat	Product consumption (gram/eating occasion)	
			average	sd
Mixed oil	NL	100	11.1	(5)
Soy oil	NL	100	11.3	(11.2)
Sunflower oil	NL	100	10.0	(8.4)
Biscuits	NL	13.9	30.8	(25)
Frites pre-fried frozen	NL	14.3	135.9	(54)
Ice cream (dairy)	NL	11.2	103.8	(64.3)
Margarine 80% fat	NL	80	13.1	(11.5)
Margarine liquid 80% fat	NL	80	7.9	(5.6)
Margarine product 60% fat	NL	60	14.8	(8.2)
Margarine product 70% fat	NL	70	15.9	(7.1)
Cold sauce (mayonnaise, dressing)	NL	70	29.8	(18.8)
Fried Food	UK	14.7	179.8	(119.7)
Ice Cream	UK	11	115.5	(66.4)
Margarine	UK	80	16.7	(9.6)
Biscuits	UK	15.4	72.3	(63.0)

^a Food consumption data were derived from the Dutch National Food Consumption Survey 2003, in this survey young adults from 19 to 30 years old were included ($n = 750$) (Hulshof et al., 2004). The National Diet and Nutrition Survey in the UK carried out between July 2000 and June 2001, was used. This survey was held among adults aged 19–64 years (<http://www.food.gov.uk/science/dietarysurveys/ndnsdocuments/>).

For the purposes of the risk assessment, all the fat in the included foods was assumed to consist of vegetable oils, which represents a worst-case situation. In the absence of consumption surveys covering specifically allergic individuals, it was assumed that users among the latter had a similar consumption pattern to non-allergic users.

2.1.3. Cross-contact scenarios

Scenarios were defined under which peanut protein could be present unintentionally in food products manufactured using refined non-peanut vegetable oils (Fig. 1). The scenarios took into account.

- The proportion of refined peanut oil production of the overall vegetable oil production in the UK, which is approx. 1% (SCOPA (<http://www.scopa.org.uk/>); personal commun).
- An estimated cross-contact percentage of refined vegetable oils with refined peanut oil during the oil refining process, that was suggested to be on average 2% (A) or a worst-case situation of 5% cross-contact (B) (FEDIOL, 2009).

Given the mean and standard deviation, a distribution was created for the measured peanut concentrations. Each scenario was combined with the distribution of measured peanut protein concentrations in refined peanut oil (0.69 ± 0.3 mg peanut protein/kg), and the percentage of fat (assumed to be all in the form of vegetable oil) in each food product (Table 1) to determine the final peanut protein concentration in the selected high-fat food products.

Fig. 1 displays a schematic representation of the various scenarios.

Scenario 1: product made with a refined vegetable oil produced immediately after production of refined peanut oil.

Scenario 2: product made with a refined vegetable oil mixture of which 1% of the oils has been produced immediately after production of refined peanut oil (peanut protein concentration is 100th of that in scenario 1).

Scenario 3: separate batches of the product made with separate batches of refined vegetable oils of which 1% had been produced

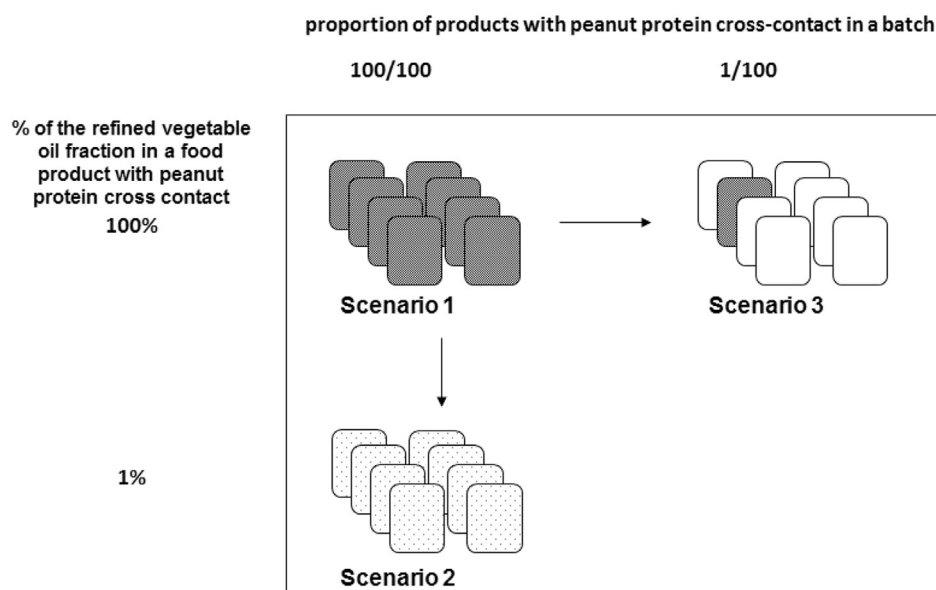


Fig. 1. The risk assessment scenarios for residues of peanut protein in food products in which peanut is not an ingredient. Food products are manufactured using refined vegetable oils after cross-contact with refined peanut oil containing peanut protein. The scenarios demonstrate the effect of changing the % refined vegetable oil (scenario 1 to 2) that in turn alters the peanut protein concentration in the food product. And the effect of the proportion of products with a peanut protein contamination (scenario 1 to 3). For each scenario two cross-contact levels were used. A corresponds with 2% cross-contact of vegetable oil with refined peanut oil, and B with a worst case situation of 5% cross-contact (not shown).

immediately after production of refined peanut oil (1% of the products will contain peanut protein residues at a concentration as in scenario 1).

For each scenario two carryover percentages were assessed: 2% (A) and 5% (B).

The advantage of probabilistic risk assessment is that it can include all available information (Madsen et al., 2009). The scenarios defined take into account the total distribution of peanut protein concentrations detected in the refined peanut oil. An additional scenario could be defined in which the production of a refined vegetable oil is preceded by refined peanut oil with one particular peanut concentration. We included this scenario by using the lowest (0.07 mg peanut protein/kg refined peanut oil) and highest concentration (1.76 mg peanut protein/kg refined peanut oil) measured in the refined peanut oil.

2.1.4. Threshold dose distribution for peanut

The peanut threshold dose distribution data reported by Taylor et al. 2014 were used for the current allergen risk assessment. Three probability distributions (Weibull, LogNormal and Log Logistic) were fitted to the 750 individual discrete dose data points for objective allergic symptoms, using the lowest (LOAELs) and no observed adverse effect levels (NOAELs) and Interval-Censoring Survival Analysis. The data were fitted to the three parametric models using the SAS LIFEREG procedure (SAS v9.3) as described previously (Taylor et al., 2009, 2014). No biological or mathematical basis exist to prefer any particular distribution and in the current risk assessment the results for all three distributions were used.

2.2. Quantitative probabilistic risk assessment

The probabilistic approach has been described in detail in other publications (Spanjersberg et al., 2007; Kruizinga et al., 2008; Madsen et al., 2009). Briefly, the probabilistic model quantifies the risk of allergic reactions using Monte Carlo simulations, with 25 runs of 10 000 iterations for each simulation. The risk is estimated based on the allergen intake calculated from the distributions for

consumption of a specific food product per eating occasion, the allergen protein concentration in that specific product and the sensitivity of the peanut-allergic population, reflected by the threshold dose distribution for peanut. The advantage is that all available quantitative information is taken into account to link allergen concentrations in food products to the risk of a reaction for the peanut allergic population. Though since statistical distributions of the parameters are used it is possible that the probabilistic modelling can predict reactions beyond the experimental data, e.g. below the lowest reported clinical thresholds (Crevel et al., 2007; Madsen et al., 2009).

The probability of an allergic reaction was estimated for the peanut-allergic user population, and was expressed as the percentage of responders within the peanut-allergic population predicted to react per eating occasion of the described food products.

2.3. Comparison with VITAL® 2.0

Action levels for peanut were derived for each food product based on the consumption of this food product and the Reference Dose for peanut protein as recommended by the expert groups of VITAL® 2.0 and ILSI Europe. Action levels guide advisory labeling decisions for the use of a precautionary warning (Taylor et al., 2014; Allen et al., 2014; Crevel et al., 2014). Action levels were derived using the mean and P95 consumption estimates for each food product and describe the maximal concentration of peanut protein that may incidentally be present unintentionally for each food product without requiring a precautionary allergen statement. The Reference Doses recommended should pose less than 1% risk of any objective reactions in the allergic consumer population (Taylor et al., 2014).

3. Results

3.1. Calculated levels of peanut protein in food products

Based on the % of fat in each food product and the distribution of peanut protein concentrations in refined peanut oil, a distribution

Table 2

Final residual peanut protein levels in two food products in each scenario. Two food products with lowest and highest average peanut protein concentration are shown together with action levels for precautionary labeling (PAL).

Scenario as described in Fig. 1	calculated level of peanut protein ($\mu\text{g}/\text{kg}$ product [ppb]) ^a	
	ice cream (11% fat)	oils (100% fat)
	Average ($\pm\text{sd}$)	Average ($\pm\text{sd}$)
1A, 3A	1.8 (0.9)	15.9 (7.6)
1B, 3B	4.4 (2.1)	39.7 (19.1)
2A	0.02 (0.01)	0.16 (0.1)
2B	0.04 (0.02)	0.40 (0.2)
VITAL [®] action levels (expressed in μg peanut protein/kg product (ppb)) ^b		
P average	1730	17750
P 95	820	5300

Note: The action levels are expressed in ppb for comparison with the low peanut protein concentration in our products. A list of action levels for each of the foods examined is presented in [Supplemental Table 1](#).

^a The final peanut protein concentration (average $\pm$ sd) in each food product is calculated using the peanut protein concentration distribution in the refined peanut oil, the different cross-contact scenarios for vegetable oils (A corresponds to 2% cross-contact, and B to 5% cross-contact) and the % fat in the food products.

^b VITAL[®] action levels were calculated from the Reference Dose for peanut 0.2 mg (Taylor et al., 2014) and the mean or 95th percentile of consumption for the food in question.

for the peanut protein levels was calculated for each food product and each scenario, including the two cross-contact levels of 2% and 5%. The highest peanut protein levels were obtained for products like oils and margarines, due to their high fat content, whereas lowest peanut protein levels were calculated for ice cream due to the relatively low content of fat in this product (approx. 11%). [Table 2](#) shows that for all scenarios the peanut protein levels in the final food products would be in the $\mu\text{g}/\text{kg}$ food range. Please note that for Sc1 and Sc3 the average protein concentration of a product will be similar, but that in Sc3 1 out of 100 products will have allergen present due to cross-contact. The distribution of the calculated levels of peanut protein in each food product was used to assess the risk for each food product under the different scenarios.

3.2. Probabilistic risk assessment

The results for the risk assessment performed are summarized in [Fig. 2](#) and [Table 3](#). The predicted number of objective allergic reactions per eating occasion ranged from 1 (0.01%) to 4 per ten thousand (0.04%) in the peanut-allergic user population in case of the LogLogistic distribution while no reactions were predicted for the LogNormal distribution ([Table 3](#)). The Weibull distribution predicted objective reactions in 1 (0.1%) to 3 per thousand (0.3%) of the allergic user populations ([Fig. 2](#)). Taylor et al. (2014) showed that the Weibull model is very conservative for all allergenic foods. In the case of peanut (and milk), the Weibull model did not accurately fit the actual data in the lower dose ranges, which are important for elaborating the Reference Dose. Thus the Weibull model was not used for the peanut Reference Dose elaboration, but we included the Weibull model in the current risk assessment to illustrate the consequences of over-conservative predictions.

The effect of changing the values of several variables in the risk assessment is shown in [Table 4](#) for the Weibull distribution. The results for the LogLogistic and Log Normal are provided in the [Supplemental Table 2](#). Reducing the cross-contact level from 5% (B) to 2% (A), the proportion of the refined vegetable oil that will come into contact with refined peanut oil (scenario 2) or the proportion of contaminated food products (scenario 3) reduced the estimated number of predicted allergic reactions in various proportions. Within a scenario, slight differences were found between the different food products; however, overall, the predicted number of objective allergic reactions within a particular scenario was within the same order of magnitude for all food products ([Table 4](#)). For example in scenario 1B, the probability of a peanut-allergic individual reacting to the various food products ranged between 1 in 1000 and 3 in a 1000 per eating occasion. In this case we used a single concentration and included only the highest peanut protein concentration measured, the risk in Sc1A increased to a maximum of 4 allergic reactions per 1000 in the peanut-allergic user

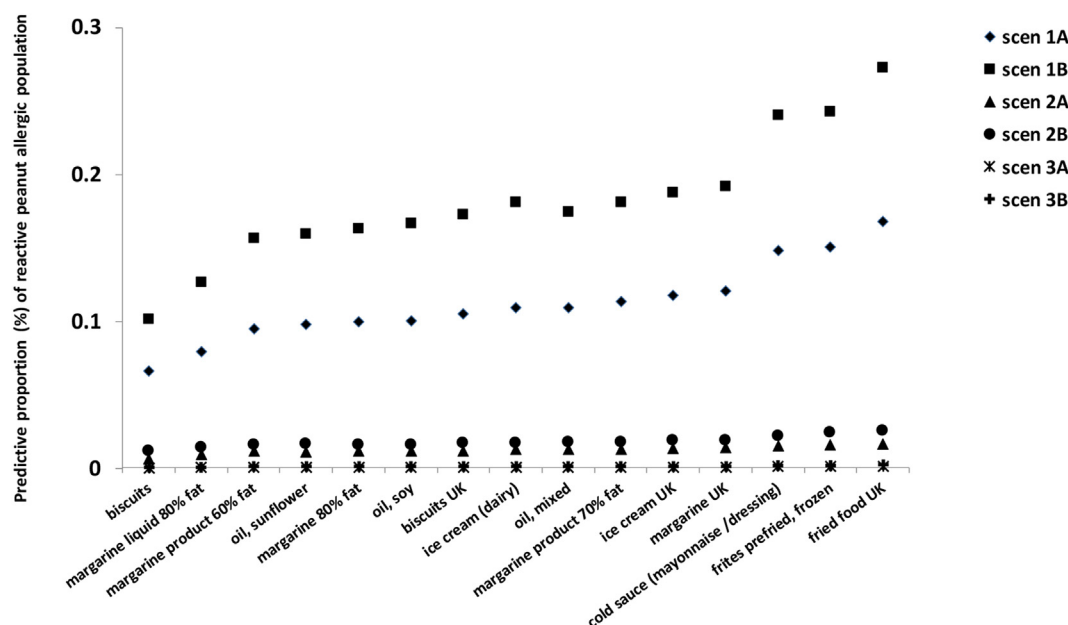


Fig. 2. Residual risk of an objective reaction in the peanut-allergic population from consumption of food products with a relative high fat content. Products have unintended peanut proteins present caused by cross-contact of refined vegetable oils with refined peanut oil. All individuals in this risk assessment are assumed to be peanut-allergic and consumers of the product of interest. Displayed are the risk data for the Weibull distribution. The risk data for LogLogistic and LogNormal are provided in the [Supplemental Table 2](#) and [Supplementary Fig. 1](#). Description of the scenarios (Sc) can be found in the Material and methods and [Fig. 1](#).

Table 3
Residual risk of an objective reaction in the peanut-allergic population predicted in 3 parametric models for worst case scenario 1B (100% Unintended Allergen Presence of refined vegetable oil, 5% cross-contact, 100/100 products). Shown is the risk from consumption of a food product with the lowest average consumption, biscuits, and the highest average consumption, fried food.

	Product consumption (gram/eating moment)		risk assessment outcome (the predicted number of reactions/million peanut-allergic individuals/eating occasion)		
	average	sd	Weibull	LogLogist	LogNormal
Biscuits	30.8	(25)	1028	112	0
Fried food	179.8	(119.7)	2728	408	0

Table 4
Residual risk of an objective reaction in the peanut-allergic population from consumption of products with unintended peanut protein for different cross-contact scenarios. Illustrated with biscuits, ice cream, mixed oil, and fried food.

Scenario description ^a	Risk assessment outcome (the predicted number of reactions/million peanut-allergic individuals/eating occasion). ^b			
	biscuits	ice cream	oil (mixed)	fried food
sc 1B (100% UAP, 5% cross-contact, 100/100 products)	1020	1816	1748	2728
sc 1A (100% UAP, 2% cross-contact, 100/100 products)	664	1096	1096	1684
sc 2B (1% UAP, 5% cross-contact, 100/100 products)	124	176	184	260
sc 2A (1% UAP, 2% cross-contact, 100/100 products)	68	136	132	172
sc 3B (100% UAP, 5% cross-contact, 1/100 products)	10	18	17	27
sc 3A (100% UAP, 2% cross-contact, 1/100 products)	7	11	11	17

^a See also detailed description in Fig. 1 of Material and Methods.

^b Selected is the risk predicted using the Weibull threshold dose distribution (the results for LogNormal and LogLogistic are provided in supplemental data).

population using the Weibull model (Fig. 3). In case the lowest peanut protein concentration measured was used, the risk was 7 in ten-thousand (0.07%).

Decreasing the cross-contact level from 5 to 2% (scenario 1B and 1A) lowers the concentration of peanut proteins in products by a factor 2.5 and leads to a smaller reduction for risk of reactions (factor 1.6).

Lowering the concentration of peanut protein in the products by a factor 100 (scenario 1 to 2) decreased the predicted number of reactions by a factor of approx 10. And reducing the proportion of products with cross-contact, scenario 3, would not alter the concentration of peanut protein within a product, but reduced the chance of picking a contaminated product from a mixed batch of products with or without unintended allergen presence. The

probability of objective allergic reactions will change proportionally with this.

Since the probabilistic modelling will *always* predict reactions as the dose distributions are not thresholded, we looked further into the doses for which the model predicted objective allergic reactions and compared these with the actual lowest clinical threshold in our substantial large threshold database. All reactions predicted by the Weibull distribution were at an average of 0.6 µg peanut protein intake (levels ranged from <1 pg to maximum of 7 µg), which is far below the lowest individual clinical threshold (75 µg of peanut protein) in the database used for the elaboration of reference doses (n = 750 individual peanut thresholds), as well as far below the reference dose proposed (200 µg of peanut protein) (Taylor et al, 2014, Allen et al., 2014) (Fig. 4). Also, most of the reactions were predicted for amounts well above the average consumption of the products.

3.3. Comparison with VITAL[®] 2.0

The Reference Doses are used in the framework of the Australian- New Zealand VITAL[®] program to permit the derivation of action levels. Selecting appropriate action levels involves a choice about the consumption parameter (average, Percentile at 95%, or another Percentile). For each scenario the levels of unintended peanut proteins were well below the action levels for each food product (Table 2). Although based on a relatively small selection of product types, the action levels for similar products (most margarines, or oils) are similar. For example, in the case of mixed oil, soy oil and sunflower oil the VITAL[®] action levels would be 17.9, 17.7 and 20 ppm respectively.

4. Discussion

Highly refined vegetable oils are widely used in the production of foods. They contain very low concentrations of residual proteins from their source (Crevel et al., 2000) and it is important to determine whether oils prepared from allergenic sources pose a risk to susceptible allergic individuals. While the European Food

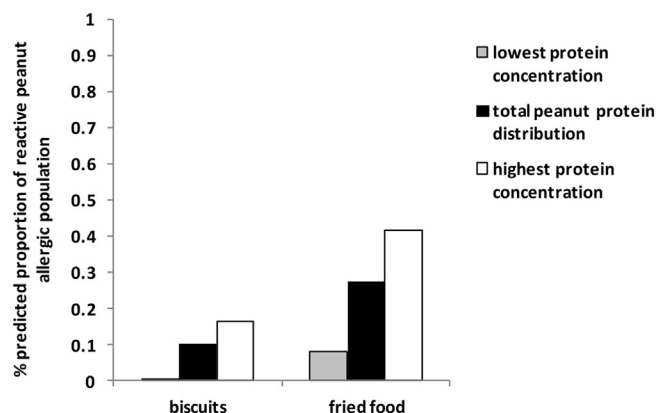


Fig. 3. The probabilistic risk assessment performed using a single peanut protein concentration. Shown is the residual risk of an objective allergic reaction in the peanut allergic population in a modification of scenario 1B (100% Unintended Allergen Presence of refined vegetable oil, 5% cross-contact, 100/100 products). Besides the total distribution, the lowest and highest peanut protein concentration were used as input for estimation of the risk for consumption of a food product with the lowest average consumption (biscuits) and the highest average consumption (fried food). The risk data for the LogLogistic and LogNormal threshold distributions are provided in Supplemental Table 3.

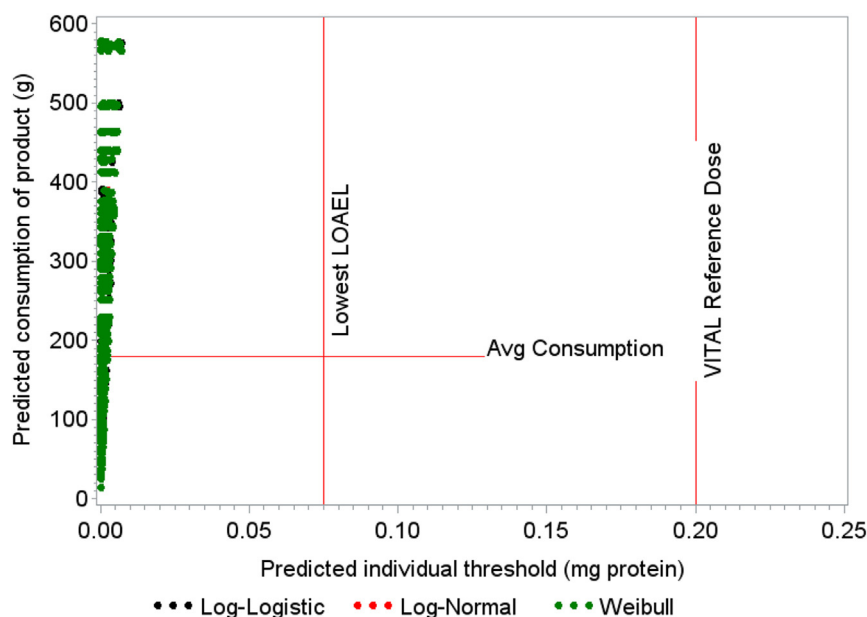


Fig. 4. Individual thresholds expressed in mg protein predicted to have a reaction in the simulation (x-axis) at the predicted consumption (y-axis) for fried food in the most worst case scenario 1B (100% UAP, 5% cross-contact, 100/100 products). Each dot represents an allergic reaction predicted by the 3 parametric models (Log logistic, Log Normal and Weibull). The most sensitive individual clinical threshold of the peanut-allergic population ($n = 750$) is displayed in the graph. Further the Reference Dose of peanut for VITAL[®] precautionary labeling guidance is shown (Allen et al., 2014; Taylor et al., 2014). The average fat consumption level for the fried food is shown.

Safety Authority concluded that highly refined soybean oil posed little risk, they considered that it is possible that peanut oil “could cause reactions in peanut-allergic individuals” (EFSA, 2004, 2007). In contrast, a well-designed controlled clinical challenge study demonstrated that highly refined peanut oil, in contrast to unrefined peanut oil, did not provoke reactions in subjects with a documented peanut allergy (Hourihane et al., 1997), substantiating the results of earlier, smaller studies (Taylor et al., 1981). As other (non-peanut) refined oils are processed on equipment on which refined peanut oil may also be processed, peanut protein residues may be present in those oils. In this study we aimed to assess the public health impact of this potential cross-contact. For the current allergen risk assessment, we estimated the predicted number of objective allergic reactions in the peanut-allergic population attributable to the presence of peanut protein residues in food products containing refined vegetable oils, other than peanut oil, as ingredients.

We used several worst case situations in the risk assessment by selecting food products with a high fat content and including a cross-contact scenario whereby the refined vegetable oils contained 5% peanut oil and assuming that the total fat fraction of a food consisted of contaminated vegetable oil. As expected, the number of predicted reactions was highest in products like pre-fried frozen frites (NL) and fried food (UK), products which contain a high proportion of fat and are eaten in large quantities, resulting in a high intake of fat. In these cases, the predicted number of objective allergic reactions in the peanut-allergic consumer population per eating occasion was estimated at a maximum of 4 allergic reactions per 1000 using the Weibull model (0.4%), the most conservative of the three models. A maximum of 4 allergic reactions per 10 000 was predicted by the Log Logistic model, whereas the Log Normal predicts no reactions for most scenarios and only 0.002% for the worst case scenario.

Probabilistic risk assessment can provide powerful insights into factors affecting risk as shown with the risk assessment in this paper, but requires circumspect interpretation of the numbers

predicted. In particular, threshold dose distributions are not thresholded, which results in prediction of reactions at doses which are unlikely to actually provoke reactions in the food allergic population. All reactions in our study were predicted to occur for doses of peanut protein ranging from <1 μ g to 7 μ g, which are at least a factor of 10 below the lowest individual clinical threshold dose in our large data set for peanut (75 μ g protein) and at least a factor of almost 30 below the Reference Dose proposed for peanut protein (Taylor et al., 2014).

In a recent publication the lowest responder of 56 peanut allergic individuals with objective symptoms was at 3 μ g peanut protein and the second most sensitive individual tolerated a dose of 30 μ g and reacted with objective symptoms at 300 μ g peanut protein (Ballmer-Weber et al., 2015), which is of the same order as the dose in our larger database. In order to reach the highest dose of 7 μ g of the most conservative prediction, much more than the average consumption of a product needs to be eaten. For example in the case of fried food this would be almost 600 g (3 times the average consumption). This indicates that it is most likely that the actual percentage of reactions, and therefore associated risks will be far below the predicted level or will even be negligible.

The presence of residual peanut proteins in refined peanut oil and their subsequent transfer by cross-contact to refined non-peanut vegetable oils may cause oil producers to apply a precautionary statement (e.g. may contain peanut), particularly if they are uncertain of potential health consequences. Food manufacturers and ingredient suppliers struggle with how to provide information on the unintended presence of allergens in ingredients. At the moment, ingredient suppliers often apply a precautionary label to their ingredients, leaving the food manufacturer uncertain of the risk associated with the food products in which the ingredient is used. This often results in precautionary labelling of the final consumer food product, while in many cases the actual concentration of allergen present in that product is very low and would not warrant a precautionary label. Such practice is not free of adverse consequences, whether through restrictions of choice or disregard

by allergic consumers of precautionary warnings which reflect an appreciable risk (Hefle et al., 2007; Pieretti et al., 2009; Cochrane et al., 2013). However, if the potential allergen protein content is provided in the communication between suppliers and food manufacturers this information is of much better value since it can be used in a quantitative risk assessment. Providing manufacturers with information on which to base a quantitative risk assessment helps them in ensuring appropriate and consistent use of precautionary allergen labeling.

5. Conclusions

In conclusion, we present a quantitative risk assessment relating to residual peanut proteins in vegetable oils, present through cross-contact. We investigated various scenarios, all of which, including worst-case scenarios, predicted low (0.4%) to negligible (0.0%) risk from these residual proteins depending on the threshold distribution model and the scenario. In particular, none would call for precautionary allergen labelling of the food products containing these oils as an ingredient, applying the VITAL[®] 2.0 Reference Doses as benchmarks. Precautionary allergen labelling is an important tool to both communicate and manage risks from unintended allergen presence, but is only effective if used judiciously. The approach we describe provides an excellent basis for decisions on the use of precautionary allergen labelling.

Funding

None.

Acknowledgement

FEDIOL, the European Vegetable Oil and Proteinmeal Association is acknowledged for providing information on the concentrations of peanut protein in samples of refined peanut oil.

Appendix A. Supplementary data

Supplementary data related to this article can be found at <http://dx.doi.org/10.1016/j.fct.2017.05.072>.

Transparency document

Transparency document related to this article can be found online at <http://dx.doi.org/10.1016/j.fct.2017.05.072>.

References

- Allen, K.A., Remington, B.C., Baumert, J.L., Crevel, R.R.W., Houben, G.F., Brooke-Taylor, S., Kruizinga, A.G., Taylor, S.L., 2014. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. *J. Allergy Clin. Immunol.* 133, 156–164. <http://dx.doi.org/10.1016/j.jaci.2013.06.042>.
- Ballmer-Weber, B.K., Fernandez-Rivas, M., Beyer, K., Defernez, M., Sperrin, M., Mackie, A.R., Salt, L.J., Hourihane, J.O.B., Asero, R., Belohlavkova, S., Kowalski, M., De Blay, F., Papadopoulos, N.G., Clausen, M., Knulst, A.C., Roberts, G., Popov, T., Sprickelman, A.B., Dubakiene, R., Vieths, S., Van Ree, R., Crevel, R., Mills, E.N.C., 2015. How much is too much? Threshold dose distributions for 5 food allergens. *J. Allergy Clin. Immunol.* 135, 964–971. <http://dx.doi.org/10.1016/j.jaci.2014.10.047>.
- Cochrane, S.A., Gowland, M.H., Sheffield, D., Crevel, R.W.R., 2013. Characteristics and purchasing behaviours of food-allergic consumers and those who buy food for them in Great Britain. *Clin. Transl. Allergy* 3, 31. <http://dx.doi.org/10.1186/2045-7022-3-31>.
- Crevel, R.W., Baumert, J.L., Baka, A., Houben, G.F., Knulst, A.C., Kruizinga, A.G., Luccioli, S., Taylor, S.L., Madsen, C.B., 2014. Development and evolution of risk assessment for food allergens. *Food Chem. Toxicol.* 67, 262–276. <http://dx.doi.org/10.1016/j.fct.2014.01.032>.
- Crevel, R.W.R., Briggs, D., Hefle, S.L., Knulst, A.C., Taylor, S.L., 2007. Hazard characterisation in food allergen risk assessment: the application of statistical approaches and the use of clinical data. *Food Chem. Toxicol.* 45 (5), 691–701. <http://dx.doi.org/10.1016/j.fct.2006.09.005>.
- Crevel, R.W.R., Kerkhoffs, M.A., Koning, M.M., 2000. Allergenicity of refined vegetable oils. *Food Chem. Toxicol.* 38 (4), 385–393.
- EFSA Panel on Dietetic Products, Nutrition and Allergies, 2004. Opinion of the Scientific Panel on Dietetic products, nutrition and allergies [NDA] related to a notification from FEDIOL and IMACE on fully refined peanut oil and fat pursuant to Article 6 paragraph 11 of Directive 2000/13/EC. *EFSA J.* 2 (11), 133. <http://dx.doi.org/10.2903/j.efsa.2004.133>.
- EFSA Panel on Dietetic Products, Nutrition and Allergies, 2007. Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from FEDIOL and IMACE on fully refined soybean oil and fat pursuant to Article 6, paragraph 11 of Directive 2000/13/EC - for permanent exemption from labelling. *EFSA J.* 5 (10), 570–579. <http://dx.doi.org/10.2903/j.efsa.2007.570>.
- FEDIOL report. Risk assessment on cross-contamination with fully refined peanut oil. Ref. 09COD018. 2009. Accessible also through the link in Code of Practice on the production and labeling of certain oils in connection with allergy (Ref. 09COD017). <http://www.fediol.be/data/09COD018Final%20Risk%20assessment%20cross%20contact.pdf>.
- Hefle, S.L., Furlong, T.J., Niemann, L., Lemon-Mule, H., Sicherer, S., Taylor, S.L., 2007. Consumer attitudes and risks associated with packaged foods having advisory labeling regarding the presence of peanuts. *J. Allergy Clin. Immunol.* 120 (1), 171–176. <http://dx.doi.org/10.1016/j.jaci.2007.04.013>.
- Hourihane, J.O.B., Bedwani, S.J., Dean, T.P., Warner, J.O., 1997. Randomised, double blind, crossover challenge study of allergenicity of peanut oils in subjects allergic to peanuts. *Br. Med. J.* 314 (7087), 1084–1088.
- Hulshof, K.F.A.M., Ocké, M.C., Van Rossum, C.T.M., Buurma-Rethans, E.J.M., Brants, H.A.M., Drijvers, J.J.M.M., Ter Doest, D., 2004. Results of the Food Consumption Survey 2003. RIVM Report No. 35003000/2004, TNO Report No. V6000. Zeist, The Netherlands.
- IFR personal communication, 2009. Extraction and Characterisation of Proteins from Peanut Oil. Norwich Research Park, Colney, Norwich NR4 7UA, UK. Confidential.
- Kruizinga, A.G., Briggs, D., Crevel, R.W., Knulst, A.C., van den Bosch, L.M., Houben, G.F., 2008. Probabilistic risk assessment model for allergens in food: sensitivity analysis of the minimum eliciting dose and food consumption. *Food Chem. Toxicol.* 46 (5), 1437–1443. <http://dx.doi.org/10.1016/j.fct.2007.09.109>.
- Madsen, C.B., Hattersley, S., Buck, J., Gendel, S.M., Houben, G.F., Hourihane, J.O.B., Mackie, A., Mills, E.N.C., Nørhede, P., Taylor, S.L., 2009. Crevel RWR: approaches to risk assessment in allergy: report from a workshop Developing a framework for assessing the risk from allergenic foods. *Food Chem. Toxicol.* 47, 480–489. <http://dx.doi.org/10.1016/j.fct.2008.12.001>.
- Moneret-Vautrin, D.A., Rance, F., Kanny, G., Olsewski, A., Gueant, J.L., Dutau, G., Guerin, L., 1998. Food allergy to peanuts in France—evaluation of 142 observations. *Clin. Exp. Allergy* 28 (9), 1113–1119.
- Office for National Statistics Social and Vital Statistics Division, Food Standards Agency, 2005. National Diet and Nutrition Survey : Adults Aged 19 to 64 Years, 2000–2001 [data collection]. UK Data Service. SN: 5140. <http://dx.doi.org/10.5255/UKDA-SN-5140-1>.
- Olsewski, A., Pons, L., Moutete, F., Aimone-Gastin, I., Kanny, G., Moneret-Vautrin, D.A., Gueant, J.L., 1998. Isolation and characterization of proteic allergens in refined peanut oil. *Clin. Exp. Allergy* 28 (7), 850–859.
- Pieretti, M.M., Chung, D., Pacenza, R., Slotkin, T., Sicherer, S.H., 2009. Audit of manufactured products: use of allergen advisory labels and identification of labeling ambiguities. *J. Allergy Clin. Immunol.* 124 (2), 337–341. <http://dx.doi.org/10.1016/j.jaci.2009.05.032>.
- Ramazzotti, M., Mulinacci, N., Pazzagli, L., Moriondo, M., Manao, G., Vincieri, F.F., Degl'Innocenti, D., 2008. Analytic investigations on protein content in refined seed oils: implications in food allergy. *Food Chem. Toxicol.* 46 (11), 3383–3388. <http://dx.doi.org/10.1016/j.fct.2008.08.005>.
- Remington, B.C., Taylor, S.L., Marx, D.B., Petersen, B.J., Baumert, J.L., 2013. Soy in wheat—contamination levels and food allergy risk assessment. *Food Chem. Toxicol.* 62, 485–491. <http://dx.doi.org/10.1016/j.fct.2013.09.013>.
- Remington, B.C., Baumert, J.L., Blom, W.M., Houben, G.F., Taylor, S.L., Kruizinga, A.G., 2015. Unintended allergens in precautionary labelled and unlabelled products pose significant risks to UK allergic consumers. *Allergy* 70 (7), 813–819. <http://dx.doi.org/10.1111/all.12625>.
- Rigby, N.M., Sancho, A.I., Salt, L.J., Foxall, R., Taylor, S., Raczynski, A., Cochrane, S.A., Crevel, R.W., Mills, E.N., 2011. Quantification and partial characterization of the residual protein in fully and partially refined commercial soybean oils. *J. Agric. Food Chem.* 59 (5), 1752–1759. <http://dx.doi.org/10.1021/jf103560h>.
- Rimbaud, L., Heraud, F., La, V.S., Leblanc, J.C., Crepet, A., 2010. Quantitative risk assessment relating to adventitious presence of allergens in food: a probabilistic model applied to peanut in chocolate. *Risk Anal.* 30 (1), 7–19. <http://dx.doi.org/10.1111/j.1539-6924.2009.01322.x>.
- Spanjersberg, M.Q., Kruizinga, A.G., Rennen, M.A., Houben, G.F., 2007. Risk assessment and food allergy: the probabilistic model applied to allergens. *Food Chem. Toxicol.* 45 (1), 49–54. <http://dx.doi.org/10.1016/j.fct.2006.07.018>.
- Taylor, S.L., Busse, W.W., Sachs, M.I., Parker, J.L., Yunginger, J.W., 1981. Peanut oil is not allergic to peanut-sensitive individuals. *J. Allergy Clin. Immunol.* 68, 372–375.
- Taylor, S.L., Crevel, R.W., Sheffield, D., Kabourek, J., Baumert, J., 2009. Threshold dose for peanut: risk characterization based upon published results from challenges of peanut-allergic individuals. *Food Chem. Toxicol.* 47 (6), 1198–1204. <http://dx.doi.org/10.1016/j.fct.2009.02.011>.

- Taylor, S.L., Baumert, J.L., Kruizinga, A.G., Remington, B.C., Crevel, R.W.R., Brooke-Taylor, S., Allen, K.J., 2014. The allergy Bureau of Australia & New Zealand, Houben G.F. Establishment of reference doses for residues of allergenic foods: report of the VITAL expert panel. *Food Chem. Toxicol.* 63, 9–17. <http://dx.doi.org/10.1016/j.fct.2013.10.032>.
- Taylor, S.L., Houben, G.F., Baumert, J.L., Crevel, R.R., Allen, K.J., Dubois, A.E., Knulst, A.C., Remington, B.C., Kruizinga, A.G., Blom, W.M., Brooke-Taylor, S., 2015. Understanding food allergen thresholds requires careful analysis of the available clinical data. *J. Allergy Clin. Immunol.* 135 (2), 583–584. <http://dx.doi.org/10.1016/j.jaci.2014.10.022>.

Supplementary material to “Assessing food allergy risks from residual peanut protein in highly refined vegetable oil” W. Marty Blom, Astrid G. Kruizinga, Carina M. Rubingh, Ben C. Remington, René W.R. Crevel and Geert F. Houben

Supplemental Table 1 VITAL® 2.0 action level for peanut protein for selected food products derived using the mean and the P95 consumption estimate for each food product and the Reference Dose of 0.2 mg for peanut (Taylor et al 2014).

Country*		Action level based on	
		Mean consumption (mg/kg food)	P95 consumption (mg/kg food)
NL	Biscuits	6.5	3.3
UK	Biscuits	2.8	1.1
NL	Cold sauce (mayonaise, dressing)	6.7	3.3
NL	Frites pre-fried frozen	1.5	0.8
UK	Fried Food	1.1	0.5
NL	Ice cream	1.9	0.8
UK	Ice Cream	1.7	0.9
NL	Margarine 80% fat	15.2	5.6
NL	Margarine liquid 80% fat	25.4	12.5
NL	Margarine product 60% fat	13.5	6.3
NL	Margarine product 70% fat	12.6	6.8
UK	Margarine UK	12.0	5.8
NL	Mixed oil	17.9	9.7
NL	Soy oil	17.8	5.3
NL	Sunflower oil	20.0	6.3

* The food consumption data from the Dutch National Food Consumption Survey 2003 (NL) or from the National Diet and Nutrition Survey 2000-2001 (UK) was used to derive the action levels.

Supplemental table 2 The residual risk estimated using the LogLogistic and Log normal threshold distribution

Residual risk of an objective reaction in the peanut-allergic population from consumption of products with unintended peanut protein for different cross-contact scenarios. Illustrated with biscuits, ice cream, mixed oil, and fried food.

Risk assessment outcome (the predicted number of reactions/million peanut-allergic individuals/ eating occasion).								
Scenario description (see Material and Methods)	LogLogistic distribution				LogNormal distribution			
	biscuits	ice cream	oil (mixed)	fried food	biscuits	ice cream	oil (mixed)	fried food
sc 1B (100% UAP, 5% cross contact, 100/100 products)	108	240	236	408	0	0	0	0
sc 1A(100% UAP, 2 % cross contact , 100/100 products)	44	128	116	216	0	0	0	0
sc 2B (1% UAP , 5% cross contact, 100/100 products)	0	0	0	4	0	0	0	0
sc 2A(1% UAP , 2% cross contact, 100/100 products)	0	0	0	0	0	0	0	0
sc 3B (100% UAP, 5% cross contact, 1/100 products)	1	2	2	4	0	0	0	0
sc 3A(100% UAP, 2% cross contact, 1/100 products)	0	1	1	2	0	0	0	0

Supplemental table S3 The risk estimated for a single peanut protein concentration.

Supplemental to Figure 3 and Table 3 of the publication the Tables S3A and S3B show the residual risk of an objective reaction in the peanut-allergic population for the scenario in which the **highest** (Supplemental table S3A) **and the lowest** (Supplemental table S3B) **peanut protein concentration** of the measured peanut protein concentrations were included in a modification of Sc1 (100% Unintended Allergen Presence of refined vegetable oil, 5% cross-contact, 100/100 products). Shown is the risk from consumption of a food product with the lowest average consumption (biscuits) and the highest average consumption (fried food) predicted in 3 parametric models of the threshold dose distribution.

Supplemental table S3A The residual risk of an objective reaction estimated for highest peanut protein concentration.

	Product consumption (gram/eating moment)		risk assessment outcome (the predicted number of reactions / million peanut-allergic individuals / eating occasion)		
	average	sd	Weibull	LogLogist	LogNormal
Biscuits	30.8	(25)	1644	180	0
fried food	179.8	(119.7)	4176	668	24

Supplemental table S3B The residual risk of an objective reaction estimated for lowest peanut protein concentration.

	Product consumption (gram/eating moment)		risk assessment outcome (the predicted number of reactions / million peanut-allergic individuals / eating occasion)		
	average	sd	Weibull	LogLogist	LogNormal
Biscuits	30.8	(25)	34	4	0
fried food	179.8	(119.7)	788	56	0

Supplemental Figure 1 Residual risk of an objective reaction in the peanut-allergic population from consumption of food products with a relative high fat content. Products have unintended peanut proteins present caused by cross-contact of refined vegetable oils with refined peanut oil. All individuals in this risk assessment are assumed to be peanut-allergic and consumers of the product of interest. Displayed are the risk data for the **LogLogistic** distribution.

