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Peanut traces in food: a probabilistic risk assessment based on the French MIRABEL survey

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RUNNING TITLE:

Allergy risk assessment of peanut traces in French food products

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TITLE

Peanut traces in food: a probabilistic risk assessment based on the French MIRABEL survey

ABSTRACT

The risk of reactions due to the unintentional presence of allergens, such as traces in packaged products, remains difficult to characterize. The aim was to assess the risk regarding unintended traces of peanut in packaged food products in peanut allergic patients using original data from the MIRABEL survey.

We developed an integrated Bayesian probabilistic risk model based on relevant data including consumption of a panel of selected products with and without precautionary labelling by peanut allergic patients, and their individual threshold dose at oral food challenge (OFC).

785 patients (< 16 years: 86%) were included in the survey. Data on OFC and food consumption were available for 238 and 443 patients, respectively. For eight food categories with precautionary labelling (30%) or without (70%), the risk was nil (no peanut traces). For chocolate tablets and spreads, the risk was not significantly different from zero. For appetizers, from the different models and including uncertainty intervals, the mean estimated risk was between 38 reactions for 1 000 000 eating occasions and 55 reactions for 10 000 eating occasions. For the 1% lowest dose reactors at OFC, the estimated risk was between 8 reactions for 10 000 and 71 reactions for 1 000 eating occasions. According to these results, the allergic risk related to peanut traces in packaged food products was only significant for the most sensitive allergic consumers of appetizers. If the link between food consumption and threshold dose is not taken into account, individual variability could be overlooked, and the risk underestimated. These findings need to be confirmed by larger and representative studies including non-packaged products.

HIGHLIGHTS

- Consumption and threshold need to be collected in a single survey to avoid risk underestimation
- From the MIRABEL results, only the most sensitive peanut allergy individuals are at risk

- Clear guidance to food industry on usage of PAL is needed
-

KEY WORDS: Accidental allergic reaction;; Peanut allergy; Precautionary labelling; Undeclared allergen; Bayesian model.

ABBREVIATIONS

CNIL: French National Data Protection Authority

ED: eliciting dose

ELISA: enzyme-linked immunosorbent assay

OFC: oral food challenge

OQALI: French Observatory of Food Quality

PAL: precautionary allergen labelling

PCR: polymerase chain reaction

DATA STATEMENT: Data available on request from the authors

AUTHOR CONTRIBUTION

Amélie Crépet: Conception and design of the survey, Acquisition of data, Methodology, Analysis and interpretation of data; Writing - Original Draft, Funding acquisition, Project management

Jocelyne Just: Interpretation of data, Review & Editing

Alexandra Papadopoulos: Acquisition of data, Analysis and interpretation of data, Review & Editing

Antoine Deschildre: Acquisition of data, Interpretation of data, Writing - Original Draft

1. INTRODUCTION

Food allergy (FA) is an increasing health concern and peanut allergy is one of the most frequent, with an estimated lifetime self-reported prevalence of 0.43% in Europe and 0.6% in French children aged 6 to 17 years (Nwaru, et al., 2014). FA management is based on the avoidance of the allergenic food and the prescription of an emergency kit in case of accidental ingestion. According to European Regulation (EU) 1169/2011 on the provision of food information to consumers, the presence of 14 ingredients, including peanut, must be listed on food labels of prepackaged foods and be declared for unpacked foods. However, a risk associated with unintended small amounts of allergens in food products still remains. In the absence of guidance and operational tools, precautionary allergen labelling (PAL) such as “may contain ” is often used on packaged foods, even when the chance of contamination and the risk to health are negligible (M. Q. Spanjersberg, A. C. Knulst, A. G. Kruizinga, G. Van Duijn, & G. F. Houben, 2010). This type of labelling leads to a real dilemma for allergic consumers (DunnGalvin, et al., 2015). Therefore, there is a need to develop operational tools and science-based guidance for appropriate labelling. This requires a quantitative risk assessment approach that considers not only the allergenic hazard but also exposure under varying conditions (Crevel, Baumert, Baka, et al., 2014; Crevel, Baumert, Luccioli, et al., 2014; Madsen, et al., 2009) and the food consumption behaviour of allergic patients (Blom, et al., 2020; Madsen, et al., 2009; Rimbaud, Heraud, La Vieille, Leblanc, & Crépet, 2010; M. Q. I. Spanjersberg, A. C. Knulst, A. G. Kruizinga, G. Van Duijn, & G. F. Houben, 2010; M. Q. I. Spanjersberg, A. G. Kruizinga, M. A. J. Rennen, & G. F. Houben, 2007).

The aim of the MIRABEL project was to develop an original and integrated framework to quantify the risk of allergic reactions to peanuts in France, Belgium and Luxembourg and to assess the concerns related to traces and precautionary labelling (Crépet, et al., 2015). The project was structured around relevant and original data on unintentional allergen traces of peanuts in selected packaged foods, the consumption behaviour of people with peanut allergy, individuals' characteristics including peanut allergic symptoms and their severity, and threshold doses for allergic reaction at oral food challenge (OFC). We chose to focus on peanut because this allergy is increasingly reported and it is one of the most commonly reported cause of severe and fatal food allergic reactions in France (Bock, Munoz-Furlong, & Sampson, 2007; Pouessel et al, 2019).

This study described the integrated probabilistic risk model developed in the MIRABEL project to estimate the risk of the peanut-allergic population. The model was based on a global Bayesian approach (Albert, Grenier, Denis, & Rousseau, 2008) applied to the original data collected in the MIRABEL survey (Crépet, et al., 2015), which made it possible to study

the relevance of integrating the link between individual threshold doses and food behaviours in the risk assessment. The risk model was applied to the two categories of food for which peanut traces were recorded, the chocolate tablets and spread and appetizers (Zagon, et al., 2015).

2. MATERIALS AND METHODS

2.1. Study design and population

The MIRABEL survey is a multi-centre survey based on the voluntary participation of 785 patients (86% < 16 years, 62% males) with peanut allergies recruited during visits by 70 allergists from France, Belgium and Luxembourg (Crépet, et al., 2015; Deschildre, et al., 2016; Guenard-Bilbault, et al., 2012; Just, et al., 2016). An anonymized standard medical questionnaire was completed by the allergists. The median age at peanut allergy diagnosis was 3 years. History of severe reactions was reported in 30% of the participants. The median peanut sIgE and rAra h2 sIgE level were 20.1 kUA/L and 11.5 kUA/L, respectively. A positive OFC was recorded for 225 patients (median ED: 67.3 mg peanut protein). Furthermore, 443 patients filled in a complete food consumption questionnaire =. The study was approved by the Ethics Committee of the French National Data Protection Authority (CNIL) (authorization no. DE-2011-048). All patients or parents signed an informed consent.

2.2. Threshold doses for peanut allergic reactions

The threshold dose distribution was modelled from the results of OFCs available for , as proposed in (Elégbédé, et al., 2019). From the different parametric distributions (Weibull, Lognormal, Loglogistic) tested with and without predictive factors in Elégbédé, et al. (2019), the Cox model with the gender, the level of rAra h 2 sIgE, the size of the skin prick test and the combination between gender and the level of rAra h 2 sIgE as predictive factors gave the best fit, followed by the Weibull with the same predictive factors. They were used to model the threshold doses distribution, as well as the Weibull model without predictive factors for comparison. All the models took into account negative OFCs which were included as censored data in the modelling.

2.3. Peanut traces in packaged food products

Ten categories of food were identified as potentially associated to PAL. They were named from the literature on the unintended presence of peanut (Rimbaud, Heraud, La Vieille, Leblanc, & Crépet, 2013) and/or from the French Observatory of Food Quality database centralizing all data provided on labels, ingredient list and precautionary labels (OQALI), (Ménard, et al., 2011). They were: breakfast cereals, cereals bars, bread and bakery products, appetizers, pizzas, cream desserts and fresh desserts, biscuits and pastry,

chocolate tablets (chocolate plain/milk/white with/without nuts, chocolate for dessert, or others chocolate tablets) or chocolate spread, other chocolate products (chocolate bars, chocolate sweets and powder chocolate) and ice cream and sorbets. Categories were divided into 52 subcategories depending of the ingredients or the flavours (chocolate; fruits, dried fruits or nuts, honey, caramel and plain, milk). A sampling plan to collect the most consumed products by the MIRABEL patients was designed. For that, an original method based on a Bayesian network was developed (Elégbédé, Papadopoulos, Gauvreau, & Crépet, 2015). The method used all the available information and several constraints to balance the total number of samples set at 899 between the different products consumed by the peanut allergic (brand, product names, labels for peanut traces). For each of the 899 products (30% with PAL), 100g picked up in three samples of the same lot were screened using a sensitive lateral flow assay with a detection limit of 2 ppm total peanut. Positive as well as suspect samples were confirmed by a real-time PCR method of comparable sensitivity. Finally, positives in both approaches were quantified by two different commercial ELISA tests (Zagon, et al., 2015).

2.4. Consumption patterns

For each of the 52 subcategories of packaged food products, patients were asked on their consumption frequency per day/week/month or year (Papadopoulos, Elegbede, Ait-Dahmane, Dubuisson, & Crépet, 2018). In case of a positive consumption, they were asked to describe the portion size using photographs and to describe the consumed products precisely by listing the brand, the product name and the ingredients. The maximum quantity consumed per eating occasion and per subcategory was calculated for each individual. The consumption of girls, boys and adults were differentiated.

2.5. Peanut allergic risk model

2.5.1. Risk model

The model integrated the following input variables: the frequency of peanut protein presence in food, the peanut protein concentration levels, the maximum consumed quantities per eating occasion, and the threshold dose of peanut protein causing an allergic reaction (Fig. 1). The model generated the exposure, the risk, and the number of allergic reactions as output variables. Each input variable was modelled with a parametric distribution (Table I), as proposed by Rimbaud, et al. (2010). The number of products with peanut traces was modelled by a binomial distribution with parameter p which was the probability of adventitious presence of peanut in the product. The occurrence of peanut in a selected food was then considered to be distributed by a Bernouilli of parameter p , the probability of the presence of

the allergen. As well, the peanut concentration C in the product was modelled by an exponential distribution with parameter λ . In a Bayesian context, priors were assigned to p and λ . A Beta (1,1) was used for p as a vague conjugate prior. For λ , an informative prior Gamma distribution around the maximum observed concentration was assigned. For food consumption, the empirical distribution of the largest amount Q of consumed product on a single eating occasion was used. The exposure was estimated by multiplying the largest consumed quantity per eating occasion Q with the peanut protein concentration level C and the probability of occurrence of peanuts in food P : $E=QxCxP$. The number of subjects reacting to a dose d was modelled with a Binomial distribution of parameter $DR(d)$, which is the probability of reaction to a dose d (see 2.5.2). The risk was then defined by $R=DR(E)$.

2.5.2. Threshold dose scenarios

The thresholds of allergic reaction were integrated into the model following three scenarios with a decreasing level of taking its link with food consumption into account (Table I). In the first scenario, S1, the link between individual threshold doses and food consumption was directly considered by allocating to each individual their corresponding observed threshold. The risk of reaction of each individual was determined by comparing their own threshold value to their exposure level. In the second scenario, S2, the link between food consumption and the individual threshold was simulated. For each individual, a threshold value was selected using predictive factors introduced in the Cox and Weibull models (Elégbédé, et al., 2019). The third one, S3, did not consider the link between food consumption and threshold of reaction. Threshold values were simulated using the Weibull model without predictive factors. Vague priors as *Normal* ($0, 10^{-3}$) and *Gamma*($10^{-3}, 10^{-3}$) were used as prior distributions of the Cox and Weibull distribution parameters (Table I). The number of individuals per scenario varied with availability of data on thresholds and individual predictive factors.

2.5.3. Computational tools

The global Bayesian model was implemented with OpenBUGS (Imperial College & Medical Research Council, UK) using the R package BRugs (R Foundation for Statistical Computing). Convergence was checked by visual analysis of two independent chains and obtained after 10 000 iterations. Another 1 000 iterations were carried out to produce posterior values for the distribution parameters and population exposure and risk. For each one of the 1000 iterations, descriptive statistics reflecting variability (mean, median, standard deviation and 2.5th, 97.5th, 99th percentiles) were estimated from population results. From the 1 000 values calculated for each statistic, the median, the 2.5th and the 97.5th percentiles were used to give estimates with 95% uncertainty intervals (UI).

3. RESULTS

3.1. Peanuts in food products, consumption and threshold doses

Peanut traces were detected in two categories of food products: in 2 (1 with PAL) out of 140 (8 with PAL) chocolate tablets and spreads and in 7 (6 with PAL) out of 58 (40 with PAL) appetizers. For chocolate tablets and spreads, the estimated probability of containing peanut traces was 1.9 [0.4, 5.1] % (Table SI of Supplementary material). The peanut protein concentration varied from 0.02 [0.01, 0.03] to 2.98 [2.69, 3.30] mg/kg. For appetizers, the estimated probability of containing peanut traces was 12.9 [6.4, 22.4] %. The peanut protein concentration varied from 0.12 [0.08; 0.17] to 16.61 [14.83; 18.48] mg/kg.

Among the 304 patients who consumed chocolate tablets and spread, the majority were children (86%) and boys (50%) (Table SII of Supplementary material). The largest mean consumed portion varies from 44g (girls) to 53.4g (adults). The largest portion was consumed by boys with 97.5th and 99th percentiles 162g and 250g. Among the 292 patients who consumed appetizers, 47% were boys. For them, the mean quantity of the largest portion was 73 g. Among the adult survey responders, 2.5% and 1% consumed more than 372 g and 862 g, respectively.

Among the 238 individuals with OFC, 1% reacted to concentrations lower than 0.19 mg peanut protein (ED1) (Table SIII of Supplementary material). The ED1 was 0.26, 0.2 and 0.08 mg peanut protein for the Cox model, and the Weibull model with and without co-variables, respectively (Elégbédé, et al., 2019). When restricting the threshold doses to the chocolate and appetizer consumers, the ED1 values were higher: 1.28 and 1.34 mg peanut protein, respectively (Table SIII of Supplementary material).

3.2. Exposure to peanuts of the MIRABEL population

The mean exposure of the 304 consumers of chocolate tablets and spreads was estimated to be 6.0×10^{-4} [0, 3×10^{-3}] mg of protein (Table II). The mean of the adult population was 10 times lower than that for children (8.0×10^{-5} mg). The estimate of the 97.5th exposure percentile was 0 [0, 0.02] mg of protein for the different populations. Positive values were found for at least 1% of the patients, but the UI95% around the 99th percentile contained the value of 0.

Adult consumers of appetizers had the highest exposure to peanut protein, with a mean of 0.05 [0.01, 0.1] mg (Table II). For the four populations, 50% of the individuals had no exposure. Positive values appeared around the 97.5th percentile; however, the lower bound of the uncertainty interval was equal to 0. The 99th percentile of the adult population was 0.7 [0.03, 7.2] mg of protein.

3.3. Impact on risk regarding the link between food consumption and threshold doses

Using individual thresholds (S1), 97.5% of the chocolate consumers (N=85) had no risk of reaction (Table III). The mean risk was $2.4 \cdot 10^{-3}$ [0, $5.9 \cdot 10^{-3}$]. For the most allergic 1%, the risk was $3.2 \cdot 10^{-2}$ [0, $8.0 \cdot 10^{-2}$]. The mean risk with the Cox model (S2) and the Weibull model with (S2) and without (S3) predictive factors was in the range of 10^{-5} and 10^{-6} . Their lower UI95% values did not contain the median estimates with the individual thresholds. The two Weibull models gave closer results to those obtained with individual thresholds, compared to the Cox model. All UI95% values contained the value of 0, indicating that estimates are not significantly different from 0.

The risk estimated from individual thresholds (S1) for appetizer consumers (N=89) was a mean of $1.1 \cdot 10^{-3}$ [0, $4.5 \cdot 10^{-3}$] (Table III). The risk equaled 0 for at least 97.5% of the individuals. The 99th percentile was $1.2 \cdot 10^{-2}$ [0, $4.8 \cdot 10^{-2}$]. With the Cox (S2) and the Weibull models with (S2) and without (S3) predictive factors, the 97.5th percentiles were different from zero. The UI95% of the 99th percentile of the three models (S2, S3) included the median estimate of this value with the individual thresholds (S1). The median estimate of the mean value with the individual thresholds (S1) was included in the UI95% values of the two Weibull models (S2, S3), but not of the Cox model (S2), which yielded lower values. The UI95% value estimated with the Cox (S2) and the two Weibull models (S2, S3) do not contain zero.

3.4. Risk and number of allergic reactions in the MIRABEL population

Extended to all chocolate consumers (N=304) and those with predictive factors (N=251), the estimated risk with the three models (Table IV) was close to that estimated for (N=85) individuals with thresholds with the same models (Table III). The median estimate of the mean risk was $2.1 \cdot 10^{-6}$, $6.0 \cdot 10^{-5}$ and $1.0 \cdot 10^{-4}$ for the Cox, and the two Weibull models, respectively. At least 97.5% of the individuals with a peanut allergy consuming chocolate tablets and spreads had a risk not significantly different from zero. Moreover, all UI95% values contained zero. Considering all appetizer consumers (N=292) and those with predictive factors (N=240), the risk was in the same range as that estimated for individuals (N=89) with thresholds with the same model. The mean risk was $1.3 \cdot 10^{-4}$, $1.7 \cdot 10^{-3}$ and $2.5 \cdot 10^{-3}$ for the Cox, and the two Weibull models, respectively. The UI95% of the mean and the 97.5th percentile did not contain zero. At least 50% of the consumers of appetizers with a peanut allergy had a risk not significantly different from zero. From the different models and including uncertainty intervals, the mean estimated risk lead to between 38 reactions for 1 000 000 eating occasions and 55 reactions for 10 000 eating occasions. For the 1% lowest dose reactors at OFC, the estimated risk lead to between 8 reactions for 10 000 and 71

reactions for 1 000 eating occasions. Mean risk was also calculated in excluding all zero values and gave similar results as the one of the P99 risk values.

4. DISCUSSION

According to the global Bayesian model applied to the data from the MIRABEL survey, the allergic risk related to peanut traces in packaged food products was only significant for the most sensitive allergic consumers of appetizers. For the other eight food categories, the risk was not significant (chocolate tablets and spreads) or nil (no peanut detected in breakfast cereals, cereals bars, bread and bakery products, pizzas, cream desserts and fresh desserts, biscuits and pastry, other chocolate products and ice cream and sorbets). Not taking into account the link between food consumption and threshold dose could result in overlooking the variability between individuals and underestimating the risk.

4.1. The global Bayesian model

The most recent risk assessment models developed for food allergy risks are based on probabilistic tools, combining parametric distributions using frequentist or Bayesian approaches in Monte Carlo simulations to estimate the risk (Biro, et al., 2019; Kruizinga, et al., 2008; Madsen, et al., 2009; B. C. Remington, Baumert, Marx, & Taylor, 2013; Rimbaud, et al., 2010; M. Q. Spanjersberg, A. G. Kruizinga, M. A. Rennen, & G. F. Houben, 2007). In the present study, we proposed a global Bayesian approach that makes it possible to integrate the variability and the uncertainty of the risk components. In most results, the uncertainty interval contained the null value, whereas the median estimate of the statistic was different from zero. This means that considering uncertainty, the statistic is not different from zero. This is an important information that provides perspective on the result obtained with the median estimate. Moreover, the global Bayesian model consists in directly estimating the final distributions of the output model variables, without needing to use second order Monte Carlo simulations. In this context, the distribution parameters of each variable are estimated conditionally to the other variables of the model. This has the advantage of facilitating future estimations of the risk when integrating subsequent data in the model or using back-calculations to test the impact of management options on the input variables. For example, with this model structure, the definition of an acceptable risk can easily be linked to the definition of an acceptable level of allergen in food. The flexibility of this type of global model also facilitates sensitivity analyses by enabling identification of the variables that most influence the allergic risk.

4.2. The relevance of integrating the link between food consumption and threshold doses

Because the food consumption of allergic consumers and/or their individual thresholds are usually unknown, the classical allergic risk assessment consists in combining consumption data of the general population with dose response models as proposed in S3 (Biro, et al., 2019; Kruizinga, et al., 2008; Madsen, et al., 2009; B. C. Remington, et al., 2013; Rimbaud, et al., 2010; M. Q. Spanjersberg, et al., 2007). The recent work of Blom, et al. (2020) comparing food consumption of general Dutch population with the consumption of 30 peanut allergic individuals concluded that no significant difference was observed. We previously found that food consumption behaviour was mainly modulated by the presence of another food allergy, and also by anxiety-related factors rather than an eliciting dose (ED) on OFC (Papadopoulos, et al., 2018). The results of the present work show that using dose-response models (S3) instead of individual thresholds (S1) could lead to an underestimation of the risk. As a result, there is a need to collect both food consumption and threshold data for allergic individuals in a single survey to improve risk assessment. When dose-response models were used, the two Weibull models gave the closest results to those using the individual thresholds. However, due to the low number of individuals in the comparison, these results must be confirmed with other analyses. Regarding scenario S2, a new approach based on Bayesian model averaging making possible to combine several survival models including predictive factors was developed and applied on various food allergens (Benjamin C. Remington, et al., 2020; Wheeler, Westerhout, Baumert, & Remington, 2021).

4.3. Risk assessment results

Regarding chocolate tablets and spreads, the risk is not significantly different from zero. For appetizer products, it cannot be ruled out for at least 2.5% of consumers. Translating the risk into the number of allergic reactions using models and UI95% values, the mean number of reactions ranged between 38 reactions for 1 000 000 eating occasions and 55 reactions for 10 000 eating occasions. Furthermore, for the 1% with the lowest ED, the number of reactions ranged between 8 for 10 000 and 71 for 1 000 eating occasions. Among those reactions, the expected rate of anaphylaxis would be 1 per 2500 reactions (Patel, et al., 2021).

These results shows a lower risk than the assessments previously carried out in Rimbaud, et al. (2013) and Rimbaud, et al. (2010). They go in the way that the detection of peanut traces has decreased over time, may be due to the improvement in allergen control. More precisely, in the MIRABEL survey, compared to Rimbaud, et al. (2013), there was a lower (or zero) presence of peanuts in food products (between 0% and 2.1% vs. 20% and 37%), lower peanut concentration levels (between 0.8 and 4.3 mg/kg of protein vs. 2.8 and

104 mg/kg of protein), and higher EDs ($ED_{1}=0.2$ vs. 0.05 mg of protein; $ED_{99}>2000$ vs. 6.4 mg of protein). In contrast, the consumed quantities were higher in the MIRABEL survey, with means of 45 and 75 g vs. 26 and 30 g for chocolate tablets and appetizer/snacks respectively, but not enough to produce positive or higher risk. The MIRABEL results must be completed by a larger including non-packaged products and representative survey in France. In particular, we are aware that peanut traces may be difficult to characterize in non-homogeneous food matrix and thus contamination can vary widely within a lot, from lot-to-lot and package-to-package.

Recently, Blom, et al. (2018) conducted a prospective study in the Netherlands in 157 adults with confirmed food allergy, and reported 151 accidental allergic reactions for 73 adults. Reactions were mainly related to the unintended presence of allergens. Packaged products represented 41% of the causative products. The main allergens were cow's milk (8 cases; 6 to 4388 mg of protein /kg of product) and peanut (6 cases; 4 to 5000 mg of protein /kg of product). Taking into account the differences between the two studies, the findings for peanut can be considered the worst-case scenario simulated with the MIRABEL models. Therefore, it is important to extend the MIRABEL survey to other foods and also other allergens, and to products other than packaged products.

4.4. Lessons learned from the MIRABEL project to improve the lives of people with peanut allergies

This study showed low frequency of unintended peanut content in a large panel of packaged food products, only observed in chocolate tablets and spreads, and in appetizer products, with and without PAL. According to these data, only the most sensitive individuals with the lowest thresholds are at risk of a reaction. They should be identified by allergists (Hourihane, et al., 2017; Turner, et al., 2016) in order to improve diet advice and treatment strategies (Baumert, Taylor, & Koppelman, 2018; B. C. Remington, Krone, & Koppelman, 2018). These results are specific to packaged products consumed by individuals with peanut allergy in France, Belgium and Luxemburg recorded in the MIRABEL survey. They cannot be extrapolated to non-packaged food, other food allergens, or populations with different consumption habits. Moreover, the fact that there is no clear distinction between products with and without PAL regarding peanut traces expresses an urgent need to provide guidance to food industry on usage of PAL.

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Table I. Prior distributions of parameters and variables of the peanut allergy risk model

	Description	Distribution or equation
Presence of allergen (p)	Number of contaminated samples among the n_1 analyzed	$x \sim Bin(n_1, p)$
	Probability of the presence of allergen (%)	$p \sim Beta(1, 1)$
	Occurrence of allergen contamination (Contaminated $P=1$ or not $P=0$)	$P \sim Bernoulli(p)$
Concentration level (C)	Parameter of the concentration distribution ($mg.kg^{-1}$), chocolate and appetizers respectively	$\lambda \sim Gamma(9225, 11389); \lambda \sim Gamma(2885, 637)$
	Allergen concentration ($mg.kg^{-1}$)	$C \sim Exp(\lambda)$
Consumption (Q)	Largest consumed portion of product(kg)	$Q \sim Empirical\ Distribution$
Dose-response (DR)	Cumulative number of subjects reacting to the dose of allergen d among n_2 patients	$F \sim Bin(n_2, DR(d))$
	Individual threshold dose (scenario 1)	-
	DR based on Cox model * (scenario 1)	Probability of reaction to the dose of allergen d $DR(d) = 1 - \exp\left(-\int_0^d h_0(u) \exp(\beta_1 Z_1 + \dots + \beta_4 Z_4) du\right)$
		Parameters of the dose-response equation $h_0(d)$ $\beta_i \sim N(0, 10^{-3})$ for $i = 1, \dots, 4$
	DR based on Weibull with covariables * (scenario 2)	Probability of reaction to the dose of allergen d $DR(d) = 1 - \exp(-b_i d^a)$
		Parameters of the dose-response equation $a \sim Gamma(10^{-3}, 10^{-3})$ $\log(b_i) = \beta_0 + \beta_1 Z_{1i} + \dots + \beta_4 Z_{pi}$ $\beta_i \sim N(0, 10^{-3})$ for $i = 0, \dots, 4$
DR based on Basic Weibull (scenario 3)	Probability of reaction to the dose of allergen d $DR(d) = 1 - \exp(-bd^a)$	
	Parameters of the dose-response equation $a \sim Gamma(10^{-3}, 10^{-3})$ $b \sim Gamma(10^{-3}, 10^{-3})$	
Exposure (E)	Exposure to peanut allergens (mg)	$E = Q \times C \times P$
Risk (R)	Risk, probability of allergic reaction (%)	$R = DR(E)$

* Dose-response was defined by covariables: Z_1 = Gender, Z_2 = level of Ara h 2 sIgE, Z_3 = size of the skin prick test, Z_4 = a interaction between the gender and the level of rAra h 2 sIgE. Details in Elégbédé, et al. (2019)

Table II. Exposure to peanut allergen of the MIRABEL patients, following the consumption of contaminated chocolate and appetizers (mg of peanut protein)

Product	Population	Estimator	Mean	SD ^a	p _{2.5} ^b	Median	p _{97.5} ^b	p ₉₉ ^b
Chocolate tablets or spread	Girls (<16 years) (n=109)	Median	0.0004	0.003	0	0	0	0.005
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	0.004	0.03	0	0	0.03	0.08
	Boys (<16 years) (n=151)	Median	0.0005	0.004	0	0	0	0.009
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	0.004	0.03	0	0	0.03	0.08
	Adults (n=44)	Median	0.00008	0.001	0	0	0	0.002
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	0.007	0.04	0	0	0.05	0.2
Total population (N = 304)	Median	0.0006	0.006	0	0	0	0.01	
	2.5% ^c	0	0	0	0	0	0	
	97.5% ^c	0.003	0.03	0	0	0.02	0.07	
Appetizers	Girls (<16 years) (n=112)	Median	0.03	0.1	0	0	0.3	0.6
		2.5% ^c	0.007	0.04	0	0	0.07	0.2
		97.5% ^c	0.1	0.7	0	0	0.9	2.1
	Boys (<16 years) (n=138)	Median	0.04	0.2	0	0	0.4	0.7
		2.5% ^c	0.01	0.06	0	0	0.09	0.2
		97.5% ^c	0.1	0.5	0	0	1.0	2.0
	Adults (n=42)	Median	0.05	0.2	0	0	0.4	0.7
		2.5% ^c	0.001	0.008	0	0	0	0.03
		97.5% ^c	0.3	1.8	0	0	1.7	7.2
Total population (N = 292)	Median	0.04	0.2	0	0	0.4	0.8	
	2.5% ^c	0.01	0.07	0	0	0.1	0.3	
	97.5% ^c	0.10	0.7	0	0	0.8	1.7	

^a standard deviation

^b 2.5th, 97.5th and 99th percentiles of the distribution

^c 2.5% and 97.5% values define a 95% uncertainty interval around the estimate with the median

Table III. Comparisons between models (S2, S3) of the predicted risk of reaction to peanut per eating occasion for MIRABEL patients with observed individual threshold dose (S1)

Products	Scenario	Estimator	Mean	SD ^a	p _{2.5} ^b	Median	p _{97.5} ^b	p ₉₉ ^b
Chocolate tablets or spread (N=85)	Individual observed thresholds (S1)	Median	2.4E-03	2.2E-02	0	0	0	3.2E-02
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	5.9E-03	5.4E-02	0	0	0	8.0E-02
	Cox model (S2)	Median	1.60E-06	1.30E-05	0	0	0	2.90E-05
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	2.30E-05	1.70E-04	0	0	1.7E-04	5.60E-04
	Weibull with predictive factors (S2)	Median	6.9E-05	5.2E-04	0	0	0	1.5E-03
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	9.4E-05	8.0E-02	0	0	1.3E-02	1.8E-01
	Weibull (S3)	Median	9.0E-05	6.9E-04	0	0	0	1.7E-03
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	5.5E-04	2.8E-03	0	0	8.0E-03	1.4E-02
Appetizers (N=89)	Individual observed thresholds (S1)	Median	1.1E-03	1.1E-02	0	0	0	1.2E-02
		2.5% ^c	0	0	0	0	0	0
		97.5% ^c	4.5E-03	4.2E-02	0	0	0	4.8E-02
	Cox model (S2)	Median	1.3E-04	5.2E-04	0	0	1.2E-03	2.3E-03
		2.5% ^c	1.9E-05	9.7E-05	0	0	8.8E-05	4.2E-04
		97.5% ^c	9.6E-04	8.0E-03	0	0	3.7E-03	1.3E-02
	Weibull with predictive factors (S3)	Median	1.8E-03	6.4E-03	0	0	1.7E-02	2.8E-02
		2.5% ^c	3.6E-04	1.8E-03	0	0	2.8E-03	7.4E-03
		97.5% ^c	6.3E-03	3.4E-02	0	0	4.5E-02	9.5E-02
	Weibull (S3)	Median	2.3E-03	7.5E-03	0	0	2.4E-02	3.3E-02
		2.5% ^c	5.1E-04	2.7E-03	0	0	6.4E-03	1.3E-02
		97.5% ^c	5.7E-03	1.8E-02	0	0	4.8E-02	7.0E-02

^a standard deviation

^b 2.5th, 97.5th and 99th percentiles of the distribution

^c 2.5% and 97.5% values define a 95% uncertainty interval around the estimate with the median

Table IV. Predicted risk of reaction to peanut per eating occasion for MIRABEL patients using the three dose-response distribution models (S2, S3)

Product	Sample size	Scenario	Estimator	Mean	SD ^a	p _{2.5} ^b	Median	p _{97.5} ^b	p ₉₉ ^b	Mean of risk values > 0
Chocolate tablets or spread	N=251	Cox model (S2)	Median	2.1E-06	2.0E-05	0	0	0	3.7E-05	3.7E-05
			2.5% ^c	0	0	0	0	0	0	0 ^d
			97.5% ^c	1.1E-05	1.1E-04	0	0	8.4E-05	2.8E-04	2.8E-04
	N=304	Weibull with predictive factors (S2)	Median	6.0E-05	5.6E-04	0	0	0	1.4E-03	1.4E-03
			2.5% ^c	0	0	0	0	0	0	0 ^d
			97.5% ^c	2.8E-04	2.1E-03	0	0	3.4E-03	8.3E-03	8.3E-03
N=240	Weibull (S3)	Median	1.0E-04	9.0E-04	0	0	0	3.3E-03	3.3E-03	
		2.5% ^c	0	0	0	0	0	0	0 ^d	
		97.5% ^c	4.2E-04	2.4E-03	0	0	6.4E-03	1.3E-02	1.3E-02	
Appetizer products	N=240	Cox model (S2)	Median	1.3E-04	6.7E-04	0	0	1.3E-03	2.5E-03	2.5E-03
			2.5% ^c	3.8E-05	2.0E-04	0	0	2.9E-04	8.0E-04	8.0E-04
			97.5% ^c	4.3E-04	3.7E-03	0	0	3.1E-03	7.4E-03	7.4E-03
	N=292	Weibull with predictive factors (S2)	Median	1.7E-03	7.0E-03	0	0	1.8E-02	3.1E-02	3.1E-02
			2.5% ^c	5.1E-04	2.6E-03	0	0	5.4E-03	1.2E-02	1.2E-02
			97.5% ^c	4.2E-03	2.4E-02	0	0	4.0E-02	6.7E-02	6.7E-02
N=292	Weibull (S3)	Median	2.5E-03	8.4E-03	0	0	2.7E-02	3.9E-02	3.9E-02	
		2.5% ^c	9.1E-04	4.2E-03	0	0	1.3E-02	2.0E-02	2.0E-02	
		97.5% ^c	5.5E-03	1.5E-02	0	0	4.9E-02	7.1E-02	7.1E-02	

^a standard deviation

^b 2.5th and 97.5th percentiles of the distribution

^c 2.5% and 97.5% values define a 95% uncertainty interval around the estimate with the median

^dno value > 0

