



Gender, prick test size and rAra h 2 sIgE level may predict the eliciting dose in patients with peanut allergy: Evidence from the Mirabel survey

Chabi Fabrice Elegbede, Alexandra Papadopoulos, Jocelyne Just, Denise Anne Moneret-Vautrin, Antoine Deschildre, Amélie Crépet

► To cite this version:

Chabi Fabrice Elegbede, Alexandra Papadopoulos, Jocelyne Just, Denise Anne Moneret-Vautrin, Antoine Deschildre, et al.. Gender, prick test size and rAra h 2 sIgE level may predict the eliciting dose in patients with peanut allergy: Evidence from the Mirabel survey. *Clinical and Experimental Allergy*, 2019, 49, pp.677-689. 10.1111/cea.13348 . hal-02291250

HAL Id: hal-02291250

<https://hal.sorbonne-universite.fr/hal-02291250>

Submitted on 18 Sep 2019

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

Gender, prick test size and rAra h 2 sIgE level may predict the eliciting dose in patients with peanut allergy: evidence from the Mirabel survey

Chabi Fabrice ELEGBEDE^{1,2}, Alexandra PAPADOPOULOS¹, Jocelyne JUST³, Denise Anne MONERET-VAUTRIN^{4,5}, Antoine DESCHILDRE⁶, Amélie CREPET^{1*}.

¹ Risk Assessment Department (DER), French Agency for Food, Environmental and Occupational Health Safety (ANSES), Maisons-Alfort, France

² French National Institute for Agricultural Research (INRA), Paris Institute of Technology for Life, Food and Environmental Sciences (AgroParisTech), UMR Economie Publique INRA-AgroParisTech, France

³ Asthma and Allergy Center, Hôpital d'Enfants Armand-Trousseau - 26, Avenue du Dr. Arnold Netter, 75571 Paris Cedex 12 – INSERM, UMR_S 1136, Sorbonne Universités, UPMC Univ Paris 06 – Institut Pierre Louis d'Epidémiologie et de Santé Publique, Equipe EPAR, 75013, Paris, France

⁴ Allergy Department, Centre Hospitalier E Durckheim, 88000 Epinal, France

⁵ Allergyvigilance Network, Vandoeuvre les Nancy, France – Lorraine University, Nancy France

⁶ CHU Lille, Pediatric Pulmonology and Allergy Department, Hôpital Jeanne de Flandre, F-59000 Lille, France

Running title: Predictive factors to determine eliciting dose in patients with peanut allergy

21 *Correspondance :

22 Amélie CREPET, ANSES, 14 rue Pierre et Marie Curie

23 94701 Maisons-Alfort cedex FRANCE27-31 avenue du Général Leclerc, MAISONS-

24 ALFORT, 94701, France

25 E-mail: amelie.crepet@anses.fr

26 Tel +33 (0)1 49 77 26 78

27 Fax +33 (0)1 49 77 38 92

28 **Acknowledgment of funding:**

29 This work was funded by the French Research Agency (ANR) under the reference ANR-10-

30 ALIA-012-01.

31

32

33

34

35

36

37 **Contributors**

38 Amélie Crépet: leader in the development and design of the MIRABEL project, involvement
39 in the formulation of hypotheses, and in the acquisition, statistical analysis and interpretation
40 of the data and in writing the manuscript.

41 Chabi Fabrice Elégbédé: involvement in statistical analysis and interpretation of the data, and
42 writing the manuscript.

43 Alexandra Papadopoulos: involvement in developing the MIRABEL project, and substantial
44 involvement in revising the manuscript prior to submission.

45 Jocelyne Just: involvement in the analysis and interpretation of the data and substantial
46 involvement in revising the manuscript prior to submission.

47 Denise-Anne Moneret-Vautrin: involvement in developing the MIRABEL project, in the
48 formulation of hypotheses, in the acquisition, analysis and interpretation of the data, and
49 substantial involvement in revising the manuscript prior to submission.

50 Antoine Deschildre: involvement in the acquisition, analysis and interpretation of the data, and
51 substantial involvement in writing the manuscript.

52 All the authors have approved the final version of the article.

53 **Abstract**

54 **Background:** Peanut allergy management is based on active avoidance and access to
55 emergency treatment including self-injectable adrenaline. Knowing the dose at which a patient
56 is likely to react is crucial for risk assessment and could significantly improve management by
57 integrating a personalized approach.

58 **Objective:** To develop a threshold dose distribution curve model from routinely collected data.

59 **Methods:** The MIRABEL survey is an observational study of 785 patients with peanut
60 allergy/sensitization conducted in France, Belgium and Luxemburg. The current analysis
61 included the 238 participants for whom medical and oral food challenge data were available.
62 Several statistical models (Kaplan-Meier, Cox model, Weibull and Lognormal with predictive
63 factors, basic Weibull and Lognormal) were compared to select the best model and predictive
64 factor combination associated with the threshold doses. Inferences were made with a Bayesian
65 approach.

66 **Results:** Patients were mainly children (mean age: 9 years [IQR: 6-11]; 87% < 16 years) and
67 males (62%). Median Ara h2 s IgE was of 8kUA/L [IQR: 1-55] and median skin prick test size
68 of 10 mm [IQR: 7-13]. OFC was positive in 204 patients (86%). The median threshold dose
69 was of 67 mg of peanut protein [IQR: 16-244]. The dose at which 1% of the patients are likely
70 to react with objective symptoms was 0.26 [0.03; 2.24] mg of peanut protein. Gender, size of
71 the skin prick test (SPT) and Ara h 2 specific IgE level had a significant impact on the threshold
72 dose distribution curve. The Cox model was the most effective to predict threshold doses with
73 this combination of factors. Girls react to lower doses than boys with a beta coefficient
74 associated to the risk and a 95% credible interval of 0.44 [0.04; 0.77]. The higher the size of
75 the SPT and the Ara h 2 specific IgE level are, the higher the risk of reacting to a small amount

of peanut, with beta coefficients associated to the risk and 95% credible intervals of 0.05 [0.02; 0.08] and 0.01 [0.01; 0.02] respectively.

Conclusion and clinical relevance: according to the model, routinely collected data could be used to estimate the threshold dose. The consequences could be the identification of high-risk patients who are susceptible to react to small amounts of peanut and a personalized management of peanut allergy integrating the risk of allergic reaction. Limitations of this study are that assessors of OFC outcome were aware of SPT and Arah2 results, and a further validation study is required to confirm the predictive value of these parameters.

Keywords

Threshold dose modeling, Eliciting dose, Peanut allergy, Predictive factors, Cox model, Risk assessment.

Abbreviations and definitions

BIC: Bayesian Information Criterion

ED_p: Eliciting Dose producing a reaction in a proportion p of the allergic population

IQR: Interquartile range

LOAEL: Lowest Observed Adverse Effect Level

NOAEL: No Observed Adverse Effect Level

OFC: Oral Food Challenge

RMSE: Root Mean Square Error

SPT: Skin Prick Test

Capsule summary

A dose distribution model including significant predictive factors improves threshold dose assessment in peanut allergic patients. Routinely collected data (gender, level of Ara h 2 sIgE and size of skin prick test) can be used by clinicians to estimate the allergic risk and consequently to personalize management.

Key messages (highlights box)

- The threshold of the allergic population is often described using only one threshold distribution curve whatever distinctive features which may be observed between the patients in the study population.
- Significant predictive factors impacting OFC threshold dose were identified and the Cox model (integrating these factors) produces the best fit of the OFC threshold distribution curve.
- Physicians could use routinely collected data to identify patients with a higher risk of reaction at low doses (high-risk patients). This approach could result in a more personalized management integrating the risk of allergic reaction.

Introduction

Patients with food allergy react to a wide range of amounts of food. The dose of food below which no reaction is observed is known as the “threshold” dose [1]. Individual thresholds can be estimated from oral food challenges (OFC), a time consuming and expensive procedure which can also cause severe reactions. Clinical threshold doses lie between the highest dose observed not to produce any adverse effect (NOAEL) and the lowest dose to produce an adverse effect (LOAEL). In practice, the threshold dose is often estimated as being the LOAEL. Thresholds can also be defined at a population level. Thus, thresholds are defined as the minimum eliciting dose (ED) which designates the amount of allergenic food to produce a reaction in a determined proportion p of the allergic population (ED $_p$). Population thresholds are characterized by fitting threshold distribution curves to individual thresholds determined by OFC. Accurately estimating a threshold at individual and population levels is crucial as it plays an important role in food allergy risk assessment and management [2, 3]. Indeed, threshold doses combined with consumed quantities and allergen concentrations in food are used by risk assessors to estimate the risk of the allergic population. [4], [5], [6] Threshold doses can also be used by risk managers to establish safe limits, i.e. a maximum amount of unintended allergen in food to protect the majority of the allergic population [7, 8]. Finally, threshold doses are essential for the allergist to make diet recommendations to their patients.

Many individual factors - such as age, gender, comorbidities, stress, effort- could impact the threshold doses and thus the associated population threshold dose distribution [9-13]. This explains why individual variability should be taken into account when modeling threshold dose distribution curves. There are only a few published studies which focus on how factors related to allergy can be combined to predict individual threshold doses and the threshold distribution curve [14]. Indeed, methods are generally based on considering the best fitting of individual thresholds by several parametric probability distributions without using predictive factors [2,

8]. Thus, the threshold of the allergic population is often described using only one threshold distribution curve whatever distinctive features may be observed between the patients in the study population.

The MIRABEL project was conducted by the French Agency for Food, Environmental and Occupational Health & Safety (ANSES) in partnership with the French National Institute for Agricultural Research (INRA) and the Allergy Vigilance Network (www.allergyvigilance.org). The objectives and the methods of the MIRABEL survey have been previously published [15, 16], as well as the characteristics of the population, mainly children (< 16 years: 86%) and primary peanut allergic patients [17, 18]. One of the objectives was to accurately define the population threshold distribution for peanut in order to assess allergic risk and to improve food labeling. This study presents an original approach to estimate threshold doses using predictive factors. The model is based on routinely collected medical data. It could be a tool for allergists to identify high-risk patients who are susceptible to react to small amounts of peanut and to improve peanut allergy management with a personalized approach integrating the risk of allergic reaction.

Materials and methods

Study design and population

The MIRABEL study is an observational multicenter survey based on the voluntary participation of patients from Metropolitan France, Belgium and Luxembourg, recruited from April 2012 to December 2013 during visits to their allergists. The 70 allergists who participated in the recruitment were affiliated to the Allergy Vigilance Network and were representative of the medical practice of all the members of the network (76% office-based and 24% hospital-based). Details have previously been described [15-18]. All the recruited patients were sensitized to

peanut (wheal diameter of skin prick test (SPT) ≥ 3 mm and/or peanut specific IgE ≥ 0.35 kUA/L). Allergic patients were those who reported an allergic reaction to peanut at their first visit to the allergist. Severe or potentially severe reactions were: anaphylactic shock, laryngeal angioedema, acute asthma, and serious systemic reaction (involving two or more organs). Non-severe reactions were: rash/dermatitis, urticarial or subcutaneous angioedema, gastro-intestinal symptoms, others. Patients without any previous clinical reaction in real life at the time of the first visit and before the OFC (if done) were considered to be sensitized rather than allergic. The study population for this analysis was the subgroup of patients for whom a peanut OFC was performed. The study was approved by the French Data Protection Authority (CNIL) (Authorization no. DE-2011-048). All patients or parents signed an informed consent.

Data collection

An anonymized standard medical questionnaire was completed by the allergists. All the collected data are described elsewhere [15-18]. The variables selected for the statistical analysis were those which could impact the threshold dose, in line with previous studies [17, 18] gender, diagnosis by the allergist at the first visit (allergy, sensitization), the age at which the OFC was performed, allergic comorbidities (atopic dermatitis, asthma, allergic rhinitis, other food allergy), and the results of the following allergic tests: wheal diameter of the SPT for peanut expressed in mm and the level of Ara h 2 sIgE expressed in kUA/L (immunoCAP system, Thermofisher, Uppsala, Sweden). Composite variables were used to distinguish patients according to the number of allergic comorbidities.

Threshold dose from oral food challenge

In this observational survey, threshold doses of peanut were obtained by single-blinded, double-blinded placebo-controlled or open OFCs, according to the French guidelines [19, 20]. The threshold dose was defined as the lowest cumulative dose of roasted crushed peanuts causing

an objective reaction, converted into mg of peanut protein (LOAEL). The OFC was considered negative in the absence of an objective reaction for a cumulative dose ≥ 7 g of peanut (1.75 g of peanut protein). The threshold dose of patients diagnosed as allergic but who did not react during an incomplete OFC were considered above the highest cumulative dose in the challenge trial, and treated as right-censored [14] in the analysis. The allergic or sensitized patients who did not react during a complete OFC and sensitized patients who did not react during an OFC which was stopped before the last incremental dose were excluded from the study to focus only on patients with confirmed allergy.

Statistical methods for threshold dose distribution modeling

Parametric Weibull, Lognormal, and Loglogistic distributions were used to model the threshold dose distribution [2]. In order to study the association of the predictive variables with the threshold doses, an approach integrating the predictive factors as covariables in the Weibull and Lognormal models was developed (Online Repository). The Cox regression model generally used in epidemiology to estimate the association between a disease and predictive factors during time [21, 22] was adapted to the allergy topic. The occurrence of the allergic reaction was considered as the disease and the threshold dose was used instead of the time(details are provided in the Online Repository). All the models were adapted to account for right censored data. First, each variable was introduced singly in the different models to test their influence on the threshold dose. Variables with a 95% confidence interval of their estimated coefficient that does not contain 0 were considered as significant. These variables were then introduced together in the models and their interactions were tested. Basic modeling of the threshold dose distribution by Weibull, Lognormal and Loglogistic distributions was also conducted in order to compare our results with literature. The models were compared using two criteria: the Bayesian Information Criterion (BIC, commonly used for model selection and which penalizes

the complexity of the models compared with the AIC), and the Root Mean Square Error (RMSE, commonly used to measure of the difference between values predicted by a model and the values observed). Inferences were performed using the Bayesian approach and were implemented in the OpenBUGS software version [23] via the BRugs package of R version 3.0.1. Simulations of the ED values from parameter estimates were done using second order Monte-Carlo simulations to separate variability and uncertainty [6] (details are provided in the Online Repository Online Repository).

Results

Study population

Overall, 785 patients were included in the MIRABEL survey [15, 17, 18]. Out of these, 280 patients underwent an OFC (open OFC: 55%) and were considered for inclusion in the present analysis. One patient who did not react during a complete OFC, 14 sensitized patients with incomplete OFC, and 27 patients with missing data were not retained. The study population thus comprised 238 patients. The allergy was confirmed by a positive OFC in 86% of cases. From the 238 patients, 29 initially considered as sensitized patients had a positive OFC (12.2%) and 34 allergic patients did not react during incomplete OFC (14.3%). The patients were mainly children (mean age at the date of the OFC: 9 years (6-11) and 87% under 16 years), and males (62%) (Table 1). The median threshold dose was of 67 mg (16-244) of peanut protein. . The minimum and the maximum threshold doses were 0.03 and 2404 mg of peanut protein, respectively.

Predictive factors of threshold doses

In univariate analysis, the level of Ara h 2 sIgE, the size of the SPT and presence of atopic dermatitis were significantly associated with the ED, whatever the model (Table 1): the greater

the SPT size and level of Ara h 2 and the absence of atopic dermatitis, the lower the ED. Gender was also significantly associated with the threshold dose for the Cox model. Table 2 presents the combination of significant predictive variables for each model. Using the Weibull and Cox models, the combination of the variables significantly influencing the threshold dose were: gender, SPT size, level of Ara h 2 sIgE and the interaction between gender and the level of Ara h 2 sIgE. The Lognormal and Loglogistic models were composed of the combination of the SPT size and the level of Ara h 2 sIgE. Figure 1 depicts that girls react to lower doses than boys for identical SPT size and level of Ara h 2 sIgE (Cox model). For a given amount of peanut protein, SPT size and level of Ara h 2 sIgE, the risk of reaction for girls is 1.22-fold higher than for boys. Figure 2(a, b) shows that the larger the SPT, the higher the risk of reacting to a small amount of peanut. Figure 2(c, d) also shows the same risk increase according to the level of Ara h 2 sIgE.

Comparison of models

Table 2 shows comparison results of the Bayesian Information Criterion (BIC) and the Root Mean Square Error (RMSE). Both clearly demonstrated that the Cox model was the best model. The BIC identified the Loglogistic models with and without predictive factors as giving the second best results, followed by the Weibull with predictive factors. In contrast, the Weibull model with and without predictive factors scored second best with the RMSE criterion followed by the Loglogistic models with predictive factors.

Predicted eliciting doses (ED_p)

The ED₀₁ calculated from the Weibull with predictive factors and Cox models were close to the Kaplan Meier estimates: respectively 0.20 [0.02; 0.99] and 0.26 [0.03; 2.24] versus 0.19 [0.03; 2.25] mg of peanut protein (Table 3), with a smaller 95% credible interval for the Weibull model. The Lognormal model with predictive factors gave a higher value for the ED₀₁ and the

highest credible interval: 1.33 [0.15; 3.93] mg of peanut protein. The Loglogistic model with predictive factors produced intermediate results: 0.89 [0.08; 3.46] mg of peanut protein. The basic Weibull, Lognormal and Loglogistic distributions produced lower values for the ED₀₁ and lower credible intervals than the ones with predictive factors: respectively 0.08 [0.03; 0.17], 0.72 [0.42; 1.14] and 0.40 [0.20; 0.74] mg of peanut protein. Similar tendencies were observed for the other ED_p values. Figure 3 shows that the threshold distribution curve estimated with the Cox model was the closest to the Kaplan-Meier estimates and that all values from Kaplan-Meier were comprised in the Cox model 95% credible interval. It can also be seen that the Weibull model with predictive factors, which produced the higher probabilities of reaction and the higher credible interval, is more conservative than the Lognormal and Loglogistic models with predictive factors. The Cox model with the highest credible interval integrates the highest part of variability. Table 3 also shows that whatever the model used, females had lower EDs than males.

Prediction of threshold dose for a given patient in clinical practice

Figure 4 shows how the threshold dose range related to a given allergic risk can be predicted for a patient from the SPT size and level of Ara h 2 sIgE using the Cox model. For example, with an SPT size of 10 mm and a level of Ara h 2 sIgE of 42 kU/L, the threshold doses triggering a reaction in 1% of the allergic females range between 0.04 and 0.89 with a median value of 0.17 mg of peanut protein. For similar values of SPT size and Ara h 2 sIgE level, the threshold doses triggering a reaction in 10% and 50% of allergic females range between [2.36, 16.1] with a median of 6.33 and [18.3, 136] with a median of 67.3 mg of peanut protein, respectively.

Discussion

Our analysis shows that the Cox model results in the best predictions of ED_p, close to the known EDs reported in the literature. The modeling we describe identifies significant predictive factors of the threshold dose in a large population, mainly children (86%: < 16 years of age), with primary peanut allergy. It is based on routinely collected medical data. This modeling could be a tool for allergists to approach allergic risk from routinely collected medical data, and consequently to better manage high-risk patients (identification of the risk to react at low doses, advices on the consumption of products with PAL, indication and procedure of OFC).

Factors influencing the threshold dose

Univariate analysis identified four variables which significantly influence the threshold dose. In fact, the female gender, a diagnosis of peanut allergy without the presence of atopic dermatitis, a high level of Ara h 2 sIgE and a large SPT size all lead to a lower threshold dose of reaction. Similarly, van der Zee et al. [14] also reported that the level of peanut sIgE and the absence of atopic dermatitis were closely associated to lower threshold doses from a study of 126 OFCs in peanut allergic children modeled by a Cox model. In contrast to our results, they also observed an age effect, with lower threshold doses for teenagers, but not a gender effect. The reason why atopic dermatitis may affect the threshold dose is not clearly understood. One hypothesis, by van der Zee, Dubois [14], is that the presence of atopic dermatitis may mask early, mild cutaneous symptoms in the setting of an OFC. Blumchen, Beder [9] used a lognormal distribution to model individual peanut thresholds from a population of 63 peanut allergic children explored with a modified OFC protocol (dose increment every 2 hours). They observed that the threshold dose was significantly and inversely correlated with peanut and Ara h 2 sIgE levels, SPT size, basophil activation, and TH2 cytokine production by peripheral blood mononuclear cells. However, symptom severity did not correlate with the threshold or any of

these markers. Finally, Santos, Du Toit [24] assessed the basophil activation test (BAT) as a means of predicting the severity and threshold of reactivity to peanut during OFCs in 124 children, including 52 with a positive OFC. They concluded that BAT can be used not only to estimate the threshold of allergic reactions during OFCs, but also the severity of the reaction. However, this result was not confirmed by Reier-Nilsen, Michelsen [25], who evaluated the accuracy of clinical and/or immunological characteristics to predict OFC reactivity threshold and the severity of the reaction in a population of 96 children (5 to 15 years old) with a history of severe allergic reactions to peanut and/or sensitization to peanut. They observed that BAT had the best accuracy to predict reactivity threshold as well as LOAEL, but not the severity of the reaction. ED was also associated to the gender, with a lowest dose in females. We have previously shown that severe peanut-allergic phenotypes were more frequent in girls [18]. McWilliam, Koplin [26] found that female adolescents of the Australian “SchoolNuts” cohort were more likely to report experiencing any adverse food reaction in the past 12 months but found no significant sex difference associated with anaphylaxis and did not show data on ED [26]. The impact of gender on ED and FA severity are lacking and our finding has to be confirmed in prospective studies.

In our study, the best model was the Cox model composed of gender, SPT size, the level of Ara h 2 sIgE and the interaction between gender and the Ara h 2 sIgE level. This interaction implies that the association between the Ara h 2 sIgE and the threshold dose is different between girls and boys. The presence of atopic dermatitis disappeared with adjustment for other variables. The fact that the combination of SPT size and Ara h 2 sIgE level is the best predictor of the threshold dose is a new concept. Several studies have been conducted to define predictive factors to diagnose peanut allergy [27-31]. Our analysis contributes to improving the prediction

of the threshold dose using a combination of routinely available data of allergic diagnosis such as Ara h 2 sIgE and SPT. These results have to be confirmed with further data and analyses.

The ED₀₁ value

The criteria used to test the goodness-of-fit concluded that the Cox model followed by the Weibull model with predictive factors is the most appropriate one to model threshold data. Taylor, Baumert [8] consented to a reference dose of 0.2 mg of peanut protein which is a consensus of ED₀₁ values estimated from 16 published studies using basic Loglogistic and Lognormal distributions. This value is close to the one obtained with the Cox model and the Weibull model and comprised in their credible intervals, which reinforce our results. The basic Weibull proposed lower ED values and the basic Lognormal and Loglogistic higher ED values. The fact that Weibull distribution produced lower values than other models has already been observed in previous studies [2, 32]. Blumchen, Beder [9] found a ED₀₅ value of 1.95 mg of peanut protein which is lower than the ones obtained with our models (around 3 mg of peanut protein except for the Weibull one at 1.4 mg peanut protein). Blom, Vlieg-Boerstra [33] reported a ED₀₅ value of 1.6 mg in a population of 135 peanut allergic children. These differences can largely be explained by the characteristics of the populations, and the differences in the OFC protocol including subjective versus objective stopping criteria, as discussed by Taylor, Houben [34].

Variability and uncertainty

Our study was multicenter and patients were recruited by both office- and hospital-based allergists. This made it possible to integrate inter-individual variability. Bayesian modeling coupled with second order Monte-Carlo simulations makes it possible to account for both inter-individual variability and model uncertainty [6]. With the basic model, the credible interval of the threshold distribution curves reflects only uncertainty, whereas with the models integrating

predictive factors, they also reflect inter-individual variability. Indeed, for fixed values of model parameters randomly selected in their distribution, a cumulative distribution function can be calculated reflecting the differences between individual threshold doses in the MIRABEL population. If this process is repeated for different values of the model parameters, a credible interval reflecting model parameter uncertainty can be estimated. When the predictive factors are taken into account, a cumulative distribution function is obtained not only for a fixed value of model parameters but also for fixed values of the factors. Therefore, the credible interval accounts both for model parameter uncertainty and inter-individual variability. However, our study has some limitations. As repeated measures of threshold dose for each patient were not available, we could not account for intra-individual variability. Moreover, patients selected to be tested by OFC might have specific characteristics and thus did not reflect general peanut allergic patients. Regarding MIRABEL patients, we did not observe any discrepancies between patients with and without OFCs, except for asthma comorbidity and age at diagnosis [17]. Due to the recruitment process, allergic individuals who did not consult allergists could not have been included in our survey and lead to selection bias. Moreover, allergists who performed the OFC were aware of the peanut sIgE or prick test results and the assessment of the reaction occurring during the OFC was not standardized. Data on individual NOAELs were not available. Therefore, it was not possible to use the method proposed by Taylor, Crevel [32] to account for the fact that the reacting dose ranges between the NOAEL and the LOAEL and not necessarily equals the LOAEL value. This could lead to an underestimation of the frequency of lower threshold doses. Finally, it is important to mention that threshold doses in this work are related to reaction by ingestion and are not appropriate to other exposure routes such as inhalation.

Consequences for medical practices and risk management

Our findings could have implications for risk assessment (threshold dose modeling), for patient management (identification of the most sensitive patients, “low threshold reactors”) and diet advice (products with precautionary labeling), OFC indications and procedure (low-dose challenge protocol, single dose protocol) and for policy makers (food labeling, precautionary allergen labeling) [35].

Integrating predictive factors by routinely collected data make it possible to integrate inter-individual variability. This is particularly significant when threshold dose modeling is used to perform risk assessment. To be conservative, it is important to consider the lower bound of the threshold dose confidence interval integrating differences between individuals instead of a median value. In the same way, this type of modeling produces a threshold dose distribution per group of allergic individuals presenting similar predictive factors as opposed to the basic modeling which only takes into account one distribution for a whole population. This is particularly relevant for clinicians giving dietary advice or to choose the OFC procedure or to modulate the dose escalation of the OFC [36, 37]. Thus, while the prediction of a threshold level with the proposed model provides additional information, it should be interpreted in the light of the patient’s clinical history and presence of other risk factors. Furthermore, it does not give information about the severity of the reaction but can be used to identify patients who are at risk of reacting to small amounts of the allergen. It is consequently a step forward to a more personalized approach, integrating allergic reaction risk [38]. Finally, our study is also important for manufacturers and public health agencies as they could use threshold doses for improving labeling practices in the food industry and developing standardized policies, and consequently increasing food safety and peanut allergic consumer confidence.

396 **Acknowledgments**

397 This work was funded by the French Research Agency (ANR) under reference ANR-10-ALIA-
398 012-01.

399 The authors wish to thank Sélina TSCHEILLER (analyst at the Allergy Vigilance Network) for
400 her contribution to the data collection and all the allergists who participated in the MIRABEL
401 survey: Dr ALT Roger, Strasbourg; BANOUN Laurence, Le Raincy ; BEAUMONT Pascale,
402 Saint Maur des Fossés ; BEGON Isabelle, Paris ; BLANCHARD Paul, Desertines ; Boix
403 Françoise, Angers ; BONNEFOY GUIONNET Bénédicte, Saint-Lo ; CHABANE Habib,
404 Saint-Denis ; CHATEAU-WAQUET Dominique, Paris ; CORDEBAR Vanina, Thionville ;
405 COUSIN Marie-Odile, Lille ; DE BLAY Frédéric, Strasbourg ; De Hauteclocque Cécile, Creil ;
406 Delaval Yvonne, Rennes; DELEBARRE-SAUVAGE Christine, Lille ; DEVOISINS Jean
407 Marc, Cholet ; DOYEN Virginie, Bruxelles ; DRON-GONZALVEZ Mireille, Martigues;
408 DROUET Martine, Angers ; DUMOND Pascale, Nancy ; DUMOULIN Anne, Brest ; DZVIGA
409 Charles, Saint Etienne ; EPSTEIN Madeleine, Paris ; FLABBEE Jenny-Anne, Thionville ;
410 FONTAINE Monique, Reims ; FRENTZ Pascale, Thionville ; GAYRAUD Jacques, Tarbes ;
411 GIBOURY LAFARGE Sophie, Verneuil sur Sein ; GRANET Patricia, Digne les Bains ;
412 Guenard-Bilbaud Lydie, Strasbourg ; HALLET Jean-Louis, Luneville ; HATAHET Riad,
413 Forbach ; Langlet Catherine, Bayonne ; Lepeltier - Canavan Laurence, Caen ; LEPRINCE
414 Françoise, Saint Quentin ; LETELLIER Edouard, Paris ; LIABEUF Valérie, Marseille ;
415 MARCHANDIN Anne, Luisant ; MASSABIE-BOUCHAT Yann-Patrick, Marseille ; Mazé
416 Marie-Hélène, Plaisir ; MENETREY Céline, Limoges ; MERCIER Valérie, Toulouse ;
417 MONSIGNY Monique, Chauny ; MOREL-CODREANU Françoise, Luxembourg ; MOUTON
418 FAIVRE Claudie, Nancy ; MULLIEZ-PETITPAS Julie, Poitiers ; NICOLAS Pascale, Poissy;
419 OUTTAS Omar, Clermont-Ferrand ; PASQUET-NOUALHAGUET Christine, Bois d'Arcy ;

420 PEROTIN-COLLARD Jeanne-Marie, Reims ; PETIT Nicolas, Verdun ; PIRSON Francoise,
421 Bruxelles ; POUVREAU Hélène, Poitiers ; PUILLANDRE Erick, Arcachon ; SABOURAUD-
422 LECLERC Dominique, Reims ; SAINT MARTIN François, Villebon sur Yvette ; SANTOS
423 Adjoke-Clarisse, Lille ; SERINGULIAN Alice, Paris ; SULLEROT Isabelle, Sens ; TERRIER
424 Patrick, Marmomme ; THIERRY Marie-Hélène, Alberville ; THIS-VAISSETTE Christine,
425 Massy ; VIGAN Martine, Besançon; VODOFF M.V, Mulhouse.

426

427 **References**

- 428 1. Crevel RWR, Ballmer-Weber BK, Taylor SL, Houben G, Mills C, Chapter five -
429 Thresholds or 'How Much Is Too Much?'. In: Madsen CB, Crevel RWR, Mills C,
430 Taylor SL eds. Risk Management for Food Allergy. San Diego: Academic Press,
431 2014;77-99.
- 432 2. Crevel RWR, Briggs D, Hefle SL, Knulst AC, Taylor SL, Hazard characterisation in
433 food allergen risk assessment: The application of statistical approaches and the use of
434 clinical data. Food and Chemical Toxicology 2007;45: 691-701.
- 435 3. Taylor SL, Hefle SL, Bindslev-Jensen C, Bock SA, Burks AW, Jr., Christie L, Hill DJ,
436 Host A, Hourihane JO, Lack G, Metcalfe DD, Moneret-Vautrin DA, Vadas PA, Rance
437 F, Skrypec DJ, Trautman TA, Yman IM, Zeiger RS, Factors affecting the determination
438 of threshold doses for allergenic foods: how much is too much? J Allergy Clin Immunol
439 2002;109: 24-30.
- 440 4. Spanjersberg MQI, Kruizinga AG, Rennen MAJ, Houben GF, Risk assessment and food
441 allergy: the probabilistic model applied to allergens. Food and Chemical Toxicology
442 2007;45: 49-54.
- 443 5. Madsen CB, Hattersley S, Buck J, Gendel SM, Houben GF, Hourihane JO, Mackie A,
444 Mills EN, Norhede P, Taylor SL, Crevel RW, Approaches to risk assessment in food
445 allergy: report from a workshop "developing a framework for assessing the risk from
446 allergenic foods". Food Chem Toxicol 2009;47: 480-9.
- 447 6. Rimbaud L, Heraud F, La Vieille S, Leblanc J-C, Crepet A, Quantitative Risk
448 Assessment Relating to Adventitious Presence of Allergens in Food: A Probabilistic
449 Model Applied to Peanut in Chocolate. Risk Analysis 2010;30: 7-19.
- 450 7. Crevel RWR, Baumert JL, Luccioli S, Baka A, Hattersley S, Hourihane JOB, Ronsmans
451 S, Timmermans F, Ward R, Chung Y-j, Translating reference doses into allergen
452 management practice: Challenges for stakeholders. Food and Chemical Toxicology
453 2014;67: 277-87.
- 454 8. Taylor SL, Baumert JL, Kruizinga AG, Remington BC, Crevel RWR, Brooke-Taylor
455 S, Allen KJ, Houben G, Establishment of Reference Doses for residues of allergenic
456 foods: Report of the VITAL Expert Panel. Food and Chemical Toxicology 2014;63: 9-
457 17.
- 458 9. Blumchen K, Beder A, Beschorner J, Ahrens F, Gruebl A, Hamelmann E, Hansen G,
459 Heinzmann A, Nemat K, Niggemann B, Wahn U, Beyer K, Modified oral food
460 challenge used with sensitization biomarkers provides more real-life clinical thresholds
461 for peanut allergy. Journal of Allergy and Clinical Immunology 2014.
- 462 10. Boulay A, Houghton J, Gancheva V, Sterk Y, Strada A, Schlegel-Zawadzka M, Sora B,
463 Sala R, Van Ree R, Rowe G, A EuroPrevall review of factors affecting incidence of
464 peanut allergy: priorities for research and policy. Allergy 2008;63: 797-809.
- 465 11. Crevel RWR, Baumert JL, Baka A, Houben GF, Knulst AC, Kruizinga AG, Luccioli S,
466 Taylor SL, Madsen CB, Development and evolution of risk assessment for food
467 allergens. Food and Chemical Toxicology 2014;67: 262-76.
- 468 12. Hourihane JOB, Grimshaw KE, Lewis SA, Briggs RA, Trewin JB, King RM, Kilburn
469 SA, Warner JO, Does severity of low-dose, double-blind, placebo-controlled food
470 challenges reflect severity of allergic reactions to peanut in the community? Clin Exp
471 Allergy 2005;35: 1227-33.
- 472 13. Hourihane JOB, Knulst AC, Thresholds of allergenic proteins in foods. Toxicology and
473 Applied Pharmacology 2005;207: 152-56.

- 474 14. van der Zee T, Dubois A, Kerkhof M, van der Heide S, Vlieg-Boerstra B, The eliciting
475 dose of peanut in double-blind, placebo-controlled food challenges decreases with
476 increasing age and specific IgE level in children and young adults. *Journal of Allergy*
477 *and Clinical Immunology* 2011;128: 1031-36.
- 478 15. Crépet A, Papadopoulos A, Elegbede CF, Loynet C, Ait-Dahmane S, Millet G, Bruyères
479 O, Van der Brempt X, Marette S, Moneret-Vautrin DA, MIRABEL: an integrated
480 project for risk and cost/benefit analysis of peanut allergy. *Regulatory Toxicology and*
481 *Pharmacology* 2015;71: 178-83.
- 482 16. Guenard-Bilbault L, Moneret-Vautrin DA, Papadopoulos A, Beaumont P, Menetrey C,
483 Beaudouin E, Gayraud J, Drouet M, Sansas B, Crepet A, Allergie à l'arachide en
484 France : premiers résultats de l'étude pilote du programme MIRABEL : « Approche
485 intégrée pour l'évaluation du risque et des coûts/bénéfices liés aux allergènes
486 alimentaires ». *Revue Française d'Allergologie* 2012;52: 509-14.
- 487 17. Deschildre A, Elegbede CF, Just J, Bruyère O, Van der Brempt X, Papadopoulos A,
488 Beaudouin E, Renaudin J-M, Crépet A, Moneret-Vautrin D-A, Peanut allergic patients
489 in the MIRABEL survey: comorbidities and specificities of eliciting dose in real-life.
490 *Clinical and experimental allergy* 2016;4: 610-20.
- 491 18. Just J, Elegbede CF, Deschildre A, Bousquet J, Moneret-Vautrin D-A, Crépet A, study-
492 group M, Two severe peanut-allergy phenotypes with gender difference: Evidence from
493 the MIRABEL survey. *Clinical and Experimental Allergy* 2016;46: 1596–604.
- 494 19. Santos C, Deschildre A, Paty E, Couderc L, Marguet C, Rance F, Oral food challenge
495 in children: who, when, and how? *Procedures Revue Française d'Allergologie et*
496 *d'Immunologie Clinique* 2006;46: 659–69
- 497 20. Fauquert JL, Deschildre A, Sabouraud D, Rancé F, Oral food challenge in children:
498 who, when, and how? Interpretation. *Revue Française d'Allergologie et d'Immunologie*
499 *Clinique* 2006;46: 470-74.
- 500 21. Hosmer J, David W., Lemeshow S, May S, *Applied Survival Analysis: Regression*
501 *Modeling of Time to Event Data*. 2nd Edn, 2008.
- 502 22. Cox DR, *Regression Models and Life Tables (with Discussion)*. *Journal of the Royal*
503 *Statistical Society, Series B* 1972;34: 187-220.
- 504 23. Lunn D, Spiegelhalter D, Thomas A, Best N, The BUGS project: Evolution, critique
505 and future directions. *Statistics in Medicine* 2009;28: 3049-67.
- 506 24. Santos AF, Du Toit G, Douiri A, Radulovic S, Stephens A, Turcanu V, Lack G, Distinct
507 parameters of the basophil activation test reflect the severity and threshold of allergic
508 reactions to peanut. *Journal of Allergy and Clinical Immunology* 2015;135: 179-86.
- 509 25. Reier-Nilsen T, Michelsen MM, Lødrup Carlsen KC, Carlsen KH, Mowinckel P,
510 Nygaard UC, Namork E, Borres MP, Håland G, Predicting reactivity threshold in
511 children with anaphylaxis to peanut. *Clinical & Experimental Allergy* 2017;DOI:
512 10.1111/cea.13078.
- 513 26. McWilliam VL, Koplin JJ, Field MJ, Sasaki M, Dharmage SC, Tang MLK, Sawyer SM,
514 Peters RL, Allen KJ, Self-reported adverse food reactions and anaphylaxis in the
515 SchoolNuts study: A population-based study of adolescents. *Journal of Allergy and*
516 *Clinical Immunology* 2018;141: 982-90.
- 517 27. Codreanu F, Collignon O, Roitel O, Thouvenot B, Sauvage C, Vilain AC, Cousin MO,
518 Decoster A, Renaudin JM, Astier C, Monnez JM, Vallois P, Morisset M, Moneret-
519 Vautrin DA, Brulliard M, Ogier V, Castelain MC, Kanny G, Bihain BE, Jacquenet S, A
520 Novel Immunoassay Using Recombinant Allergens Simplifies Peanut Allergy
521 Diagnosis. *International Archives of Allergy and Immunology* 2011;154: 216-26.

28. DunnGalvin A, Daly D, Cullinane C, Stenke E, Keeton D, Erlewyn-Lajeunesse M, Roberts GC, Lucas J, Hourihane JOB, Highly accurate prediction of food challenge outcome using routinely available clinical data. *Journal of Allergy and Clinical Immunology* 2011;127: 633-39.e3.
29. Klemans RJB, Broekman HCHP, Knol EF, Bruijnzeel-Koomen CAFM, Otten HG, Pasmans SGMA, Knulst AC, Ara h 2 Is the Best Predictor for Peanut Allergy in Adults. *Journal of Allergy and Clinical Immunology: In Practice* 2013;1: 632-38.e1.
30. Klemans RJB, Otte D, Knol M, Knol EF, Meijer Y, Gmelig-Meyling FHJ, Bruijnzeel-Koomen CAFM, Knulst AC, Pasmans SGMA, The diagnostic value of specific IgE to Ara h 2 to predict peanut allergy in children is comparable to a validated and updated diagnostic prediction model. *Journal of Allergy and Clinical Immunology* 2013;131: 157-63.
31. Nicolaou N, Murray C, Belgrave D, Poorafshar M, Simpson A, Custovic A, Quantification of specific IgE to whole peanut extract and peanut components in prediction of peanut allergy. *Journal of Allergy and Clinical Immunology* 2011;127: 684-85.
32. Taylor SL, Crevel RWR, Sheffield D, Kabourek J, Baumert J, Threshold dose for peanut: Risk characterization based upon published results from challenges of peanut-allergic individuals. *Food and Chemical Toxicology* 2009;47: 1198-204.
33. Blom WM, Vlieg-Boerstra BJ, Kruizinga AG, van der Heide S, Houben GF, Dubois AEJ, Threshold dose distributions for 5 major allergenic foods in children. *Journal of Allergy and Clinical Immunology* 2013;131: 172-79.
34. Taylor SL, Houben GF, Baumert JL, Crevel RRWR, Allen KJ, Dubois AEJ, Knulst AC, Remington BC, Kruizinga AG, Blom WM, Brooke-Taylor S, Understanding food allergen thresholds requires careful analysis of the available clinical data. *Journal of Allergy and Clinical Immunology* 2015;135: 583-84.
35. Graham F. EPA, Clinical implications of food allergen thresholds. *Clinical and Experimental Allergy* 2018;48: 632-40.
36. Cochrane SA, Salt LJ, Wantling E, Rogers A, Coutts J, Ballmer-Weber BK, Development of a standardized low-dose double-blind placebo-controlled challenge vehicle for the EuroPrevall project. *Allergy* 2012;67: 107-13.
37. Hourihane JOB, Allen KJ, Shreffler WG, Dunngalvin G, Nordlee JA, Zurzolo GA, Dunngalvin A, Gurrin LC, Baumert JL, Taylor SL, Peanut Allergen Threshold Study (PATS): Novel single-dose oral food challenge study to validate eliciting doses in children with peanut allergy. *Journal of Allergy and Clinical Immunology* 2017;139: 1583-90.
38. Deschildre A, Lejeune S, Cap M, Flammarion S, Jouannic L, Amat F, Just J, Food allergy phenotypes: The key to personalized therapy. *Clinical & Experimental Allergy* 2017;47: 1125-37.

Table 1: OFC results, patients characteristics and allergy tests (sIgE¹, skin prick test) : associations with the threshold dose

OFC results, patients characteristics and allergy tests	Values	Association with the threshold dose			
		Weibull	Lognormal	Loglogistic	Cox
		95% CI ⁽²⁾	95% CI ⁽²⁾	95% CI ⁽²⁾	95% CI ⁽²⁾
Oral food challenges					
- Positive, n (%)					
- Threshold dose mg of peanut protein					
Median (IQR) ⁽¹⁾	204 (86)84 (16 - 244)				
[0; 5[, n (%)	19 (8)				
[5; 50[, n (%)	71 (30)				
[50; 100[, n (%)	35 (15)				
[100; 1000[, n (%)	92 (38)				
≥1000, n (%)	21 (9)				
Age at OFC (year)					
Median (IQR)	8 (6 - 11)	[-0.04; 0.03]	[-0.09; 0.04]	[-0.08; 0.03]	[-0.04; 0.03]
Min -, Max	2 - 27				
Gender (males), n (%)	147 (62)	[-0.02; 0.55]	[-0.95; 0.15]	[-0.98; 0.07]	[0.01; 0.57]
Confirmed diagnosis of peanut allergy, n (%)	209 (88)	[-0.46; 0.31]	[-1.02; 0.60]	[-0.94; 0.55]	[-0.4; 0.38]
Allergic comorbidities					
- Atopic dermatitis, n (%)	162 (68)	[-0.62; -0.04]	[0.02; 1.18]	[0.08; 1.18]	[-0.63; -0.05]
- Asthma, n (%)	155 (65)	[-0.30; 0.26]	[-0.47; 0.64]	[-0.53; 0.54]	[-0.33; 0.25]
- Rhinitis, n (%)	130 (55)	[-0.45; 0.08]	[-0.34; 0.76]	[-0.26; 0.80]	[-0.47; 0.08]
- Other food allergy, n (%)	148 (62)	[-0.46; 0.07]	[-0.41; 0.74]	[-0.25; 0.86]	[-0.5; 0.06]
- Atopic dermatitis + Asthma, n (%)	107 (45)	[-0.47; 0.11]	[-0.23; 0.87]	[-0.26; 0.88]	[-0.47; 0.08]
- Atopic dermatitis + Asthma + Other food allergy, n (%)	77 (32)	[-0.47; 0.11]	[-0.36; 0.87]	[-0.24; 0.87]	[-0.49; 0.10]
Specific IgE to Ara h 2 (kUA/L),					
Median (IQR)	8 (1 - 55)	[0.01; 0.02]	[-0.03; -0.01]	[-0.03; -0.01]	[0.01; 0.02]
Min - Max	0.01 - 101				
Skin prick tests size (mm)					
Median (IQR)	10 (7 - 13)	[0.04; 0.09]	[-0.15; -0.05]	[-0.14; -0.06]	[0.04; 0.10]

Min - Max	0.01 - 30				
-----------	-----------	--	--	--	--

⁽¹⁾ slgE: specific IgE, IQR = Interquartile range.

⁽²⁾ 95% CI: the credible interval defined by the 2.5th and the 97.5th percentiles of the parameter distribution associated with each predictive variable. Boldfaced text indicates statistical significance. The variable is significantly associated with threshold dose if the 95% CI does not contain 0. For the Weibull and Cox models, a positive confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk. For the Lognormal and Loglogistic models, a negative confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk.

Table 2: Significant predictive variables, model parameter estimates and criteria to compare models

	Model parameters		Mean	95% CI ⁽¹⁾	BIC ⁽⁴⁾	RMSE ⁽⁵⁾
Weibull with covariables $d \sim \text{Weibull}(a, b_i)$ $F(d; a, b_i) = 1 - \exp(-b_i d^a)$	a		0.65	[0.58; 0.72]	2687 [2667; 2713]	528 [515; 564]
	$\log(b_i) =$	β_0 (Intercept)	-4.45	[-5.04; -3.87]		
		β_1 (Gender)	0.42	[0.04; 0.78]		
		β_2 (SPT)	0.05	[0.02; 0.07]		
		β_3 (Ara h 2)	0.01	[0.01; 0.02]		
		β_4 (Gender * Ara h 2)	-0.01	[-0.01; -1 e-04]		
Lognormal with covariables ⁽²⁾ $d \sim \text{Lognormal}(\mu_i, \sigma)$ $F(d; \mu, \sigma) = \Phi\left(\frac{\ln(d) - \mu_i}{\sigma}\right)$	$\mu_i =$	β_0 (Intercept)	5.74	[5.17; 6.3]	2701 [2680; 2726]	731 [554; 1249]
		β_1 (SPT)	-0.07	[-0.11; -0.02]		
		β_2 (Ara h 2)	-0.02	[-0.02; -0.01]		
	σ		1.92	[1.74; 2.12]		
Loglogistic with covariables $\ln(d) \sim \text{Logistic}(\mu_i, \sigma)$ $F(d; \mu, \sigma) = \frac{1}{1 + \exp\left(\frac{d - \mu_i}{\sigma}\right)}$	$\mu_i =$	β_0 (Intercept)	5.86	[5.33; 6.39]	2592 [2579; 2615]	595 [532; 2047]
		β_1 (SPT)	-0.07	[-0.12; -0.03]		
		β_2 (Ara h 2)	-0.02	[-0.02; -0.01]		
	σ		1.07	[0.96; 1.2]		
Cox model ⁽³⁾ $F(d) = 1 - \exp\left(\int_0^d h_0(u) \exp(\beta_1 Z_1 + \dots + \beta_4 Z_4) du\right)$	$h(d) =$	$h_0(d)$			1619 [1604; 1633]	519 [509; 541]
		β_1 (Gender)	0.44	[0.04; 0.77]		
		β_2 (SPT)	0.05	[0.02; 0.08]		
		β_3 (Ara h 2)	0.01	[0.01; 0.02]		
		β_4 (Gender * Ara h 2)	-0.01	[-0.01; -3 e-04]		
Basic Weibull $d \sim \text{Weibull}(a, b) \quad \text{---} \quad F(d; a, b) = 1 - \exp(-bd^a)$	a		0.57	[0.52; 0.63]	2720 [2699; 2746]	547 [542; 575]
	b		0.04	[0.03; 0.06]		
Basic Lognormal ⁽²⁾ $d \sim \text{Lognormal}(\mu, \sigma) \quad \text{---} \quad F(d; \mu, \sigma) = \Phi\left(\frac{\ln(d) - \mu}{\sigma}\right)$	μ		4.51	[4.23; 4.79]	2721 [2700; 2746]	732 [575; 1195]
	σ		2.08	[1.89; 2.3]		
Basic Loglogistic $\ln(d) \sim \text{Logistic}(\mu_i, \sigma) \quad \text{---} \quad F(d; \mu, \sigma) = \frac{1}{1 + \exp\left(\frac{d - \mu}{\sigma}\right)}$	μ		4.56	[4.29; 4.83]	2646 [2621; 2680]	606 [586; 611]
	σ		1.19	[1.06; 1.33]		

d : Threshold dose

⁽¹⁾ 95% CI: the credible interval defined by the 2.5th and the 97.5th percentiles of the parameter distribution associated with each predictive variable. The variable is significantly associated with the threshold dose if the 95% CI does not contain 0. For the Weibull and Cox models, a positive confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk. For the Lognormal and Loglogistic models, a negative confidence interval of the parameter indicates a negative association with the threshold dose value and thus a positive association with the risk.

- ⁽²⁾ Φ : the cumulative distribution function of the standard normal distribution.
⁽³⁾ $h_0(d)$: the baseline hazard, as defined in the repository material.
⁽⁴⁾ BIC: Bayesian Information Criteria, the lower the BIC value, the best the model
⁽⁵⁾ RMSE: Root Mean Square Error, the lower the RMSE value, the best the model

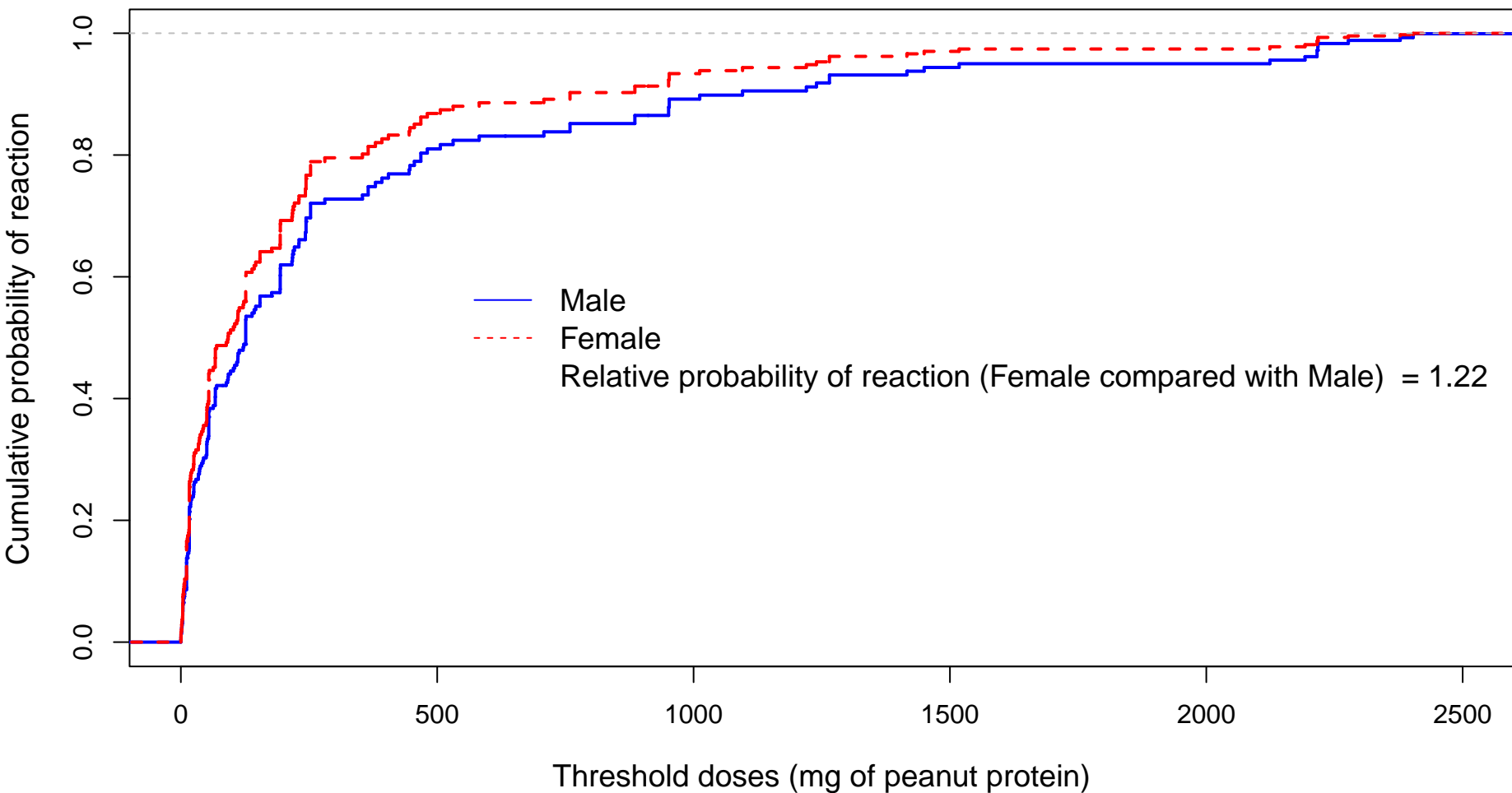
Table 3: Eliciting doses (ED_p in mg of peanut protein) triggering an allergic reaction for p% of the population. The ED_p are described by their median and the 2.5th and 97.5th percentiles. These percentiles define a 95% credible interval around the median estimate. The interval integrates all values for predictive variables and for model parameters.

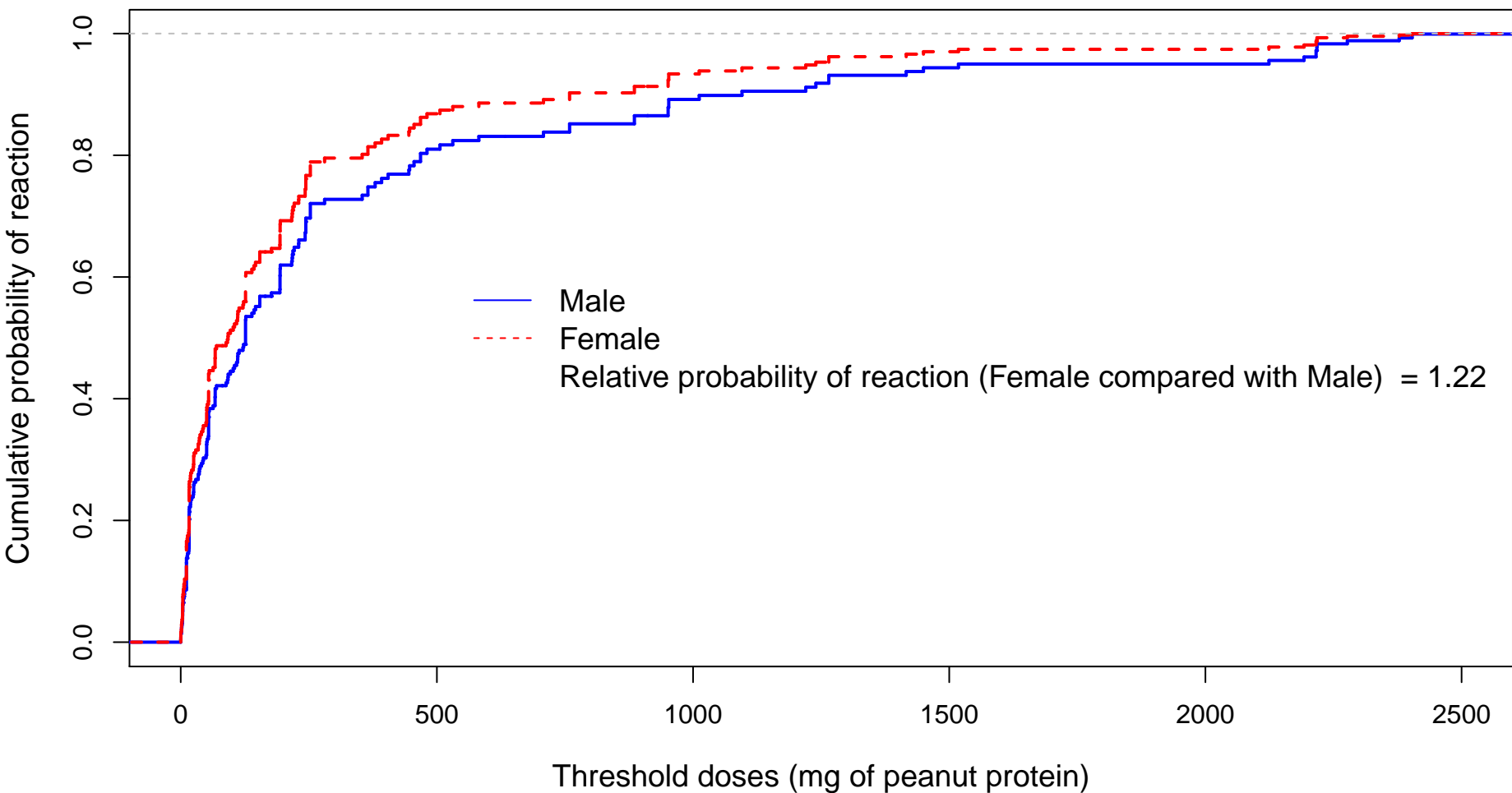
	Models	Estimator	ED _p						
			1	5	10	50	90	95	99
Entire population	Kaplan Meier	Median	0.19	3.62	8.13	126	1455	2218	2392
		2.5 th percentile	0.03	1.81	4.00	89.8	1055	2143	2321
		97.5 th percentile	2.25	5.97	11.1	177	2218	NA	NA
	Weibull with covariables	Median	0.20	2.58	7.94	149	962	1448	2830
		2.5 th percentile	0.02	0.32	1.03	20.7	136	204	393
		97.5 th percentile	0.99	11.0	32.3	567	3692	5612	11056
	Lognormal with covariables	Median	1.33	5.17	10.7	135	1653	3349	12562
		2.5 th percentile	0.15	0.58	1.20	15.3	188	382	1426
		97.5 th percentile	3.93	14.2	28.5	343	4454	9352	38011
	Log-logistic with covariables	Median	0.89	5.37	12.1	132	1422	3165	18770
		2.5 th percentile	0.08	0.51	1.15	12.7	136	302	1737
		97.5 th percentile	3.46	18.9	42.1	441	5014	11731	76115
	Cox model	Median	0.26	3.9	11.1	127	1244	2191	2218
		2.5 th percentile	0.03	0.94	2.93	16.4	126	194	251
		97.5 th percentile	2.24	11.1	25.0	676	2389	2400	2403
	Basic Weibull	Median	0.08	1.38	4.94	137	1144	1817	3896
		2.5 th percentile	0.03	0.74	2.96	105	891	1377	2789
		97.5 th percentile	0.17	2.39	7.77	176	1526	2479	5556
	Basic Lognormal	Median	0.72	3.08	6.74	104	1597	3472	14841
		2.5 th percentile	0.42	1.99	4.53	78.8	1079	2224	8457
		97.5 th percentile	1.14	4.46	9.23	135	2510	5863	28724
	Basic Loglogistic	Median	0.40	2.98	7.47	108	1576	3890	28998
		2.5 th percentile	0.20	1.84	4.96	83.1	1069	2461	15442
		97.5 th percentile	0.74	4.68	10.88	145	2534	6880	62987

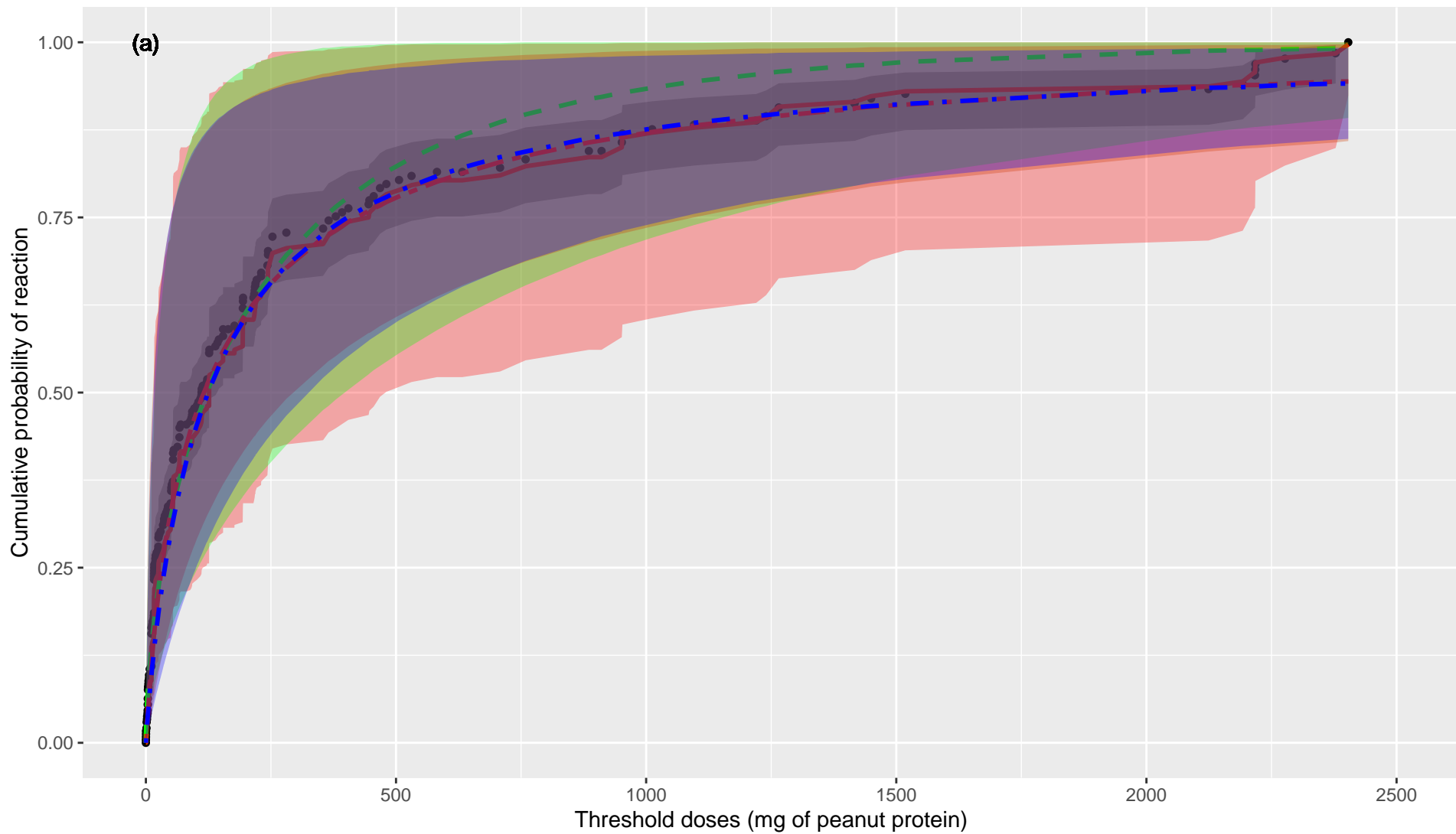
According to gender	Kaplan Meier (Female)	Median	0.03	3.22	6.32	64.7	752	1444	2218
		2.5 th percentile	0.01	0.24	3.65	49.1	457	739	2011
		97.5 th percentile	3.74	10.68	14.9	125	NA	NA	NA
	Kaplan Meier (Male)	Median	0.22	3.54	7.96	153	2198	2276.	2396
		2.5 th percentile	0.07	1.61	3.81	113	1238	2204	2372
		97.5 th percentile	2.99	7.78	12.3	218	NA	NA	NA
	Weibull with covariables (Female)	Median	0.14	1.75	5.44	104	674	1015	1980
		2.5 th percentile	0.03	0.39	1.26	25.6	169	254	494
		97.5 th percentile	0.50	5.35	15.4	264	1708	2592	5152
	Weibull with covariables (Male)	Median	0.29	3.90	12.2	237	1534	2300	4464
		2.5 th percentile	0.02	0.30	0.94	18.2	117	177	339
		97.5 th percentile	1.10	11.9	34.6	608	4011	6083	12072
	Lognormal with covariables (Female)	Median	1.26	4.85	9.95	124	1491	3014	11264
		2.5 th percentile	0.15	0.59	1.22	15.4	184	369	1354
		97.5 th percentile	3.63	13.2	26.2	315	4064	8600	35195
	Lognormal with covariables (Male)	Median	1.44	5.61	11.6	145	1752	3534	13148
		2.5 th percentile	0.15	0.59	1.22	15.6	192	387	1441
		97.5 th percentile	4.01	14.4	28.7	342	4463	9396	38538
	Loglogistic with covariables (Female)	Median	0.59	3.60	8.09	88.2	944	2101	12210
		2.5 th percentile	0.07	0.44	1.00	11.0	116	252	1408
		97.5 th percentile	2.20	11.9	26.1	268	3011	6974	46166
	Loglogistic with covariables (Male)	Median	1.16	7.17	16.3	179	1920	4316	25084
		2.5 th percentile	0.12	0.77	1.75	19	202	446	2566
		97.5 th percentile	3.78	21.33	46.5	483	5378	12457	80017
	Cox model (Female)	Median	0.19	3.63	8.29	98.5	828	1250	2218
		2.5 th percentile	0.03	1.26	3.36	16.4	127	217	446
		97.5 th percentile	0.96	6.33	15.8	230	2217	2318	2400
	Cox model (Male)	Median	0.68	6.10	13.5	220	2210	2270	2218
		2.5 th percentile	0.03	0.50	2.41	16.4	111	149	194
		97.5 th percentile	2.40	12.6	25.5	755	2392	2401	2403
	Basic Weibull (Female)	Median	0.07	1.11	3.82	95.3	735	1149	2383
		2.5 th percentile	0.02	0.41	1.65	62.1	508	760	1519
		97.5 th percentile	0.24	2.70	7.83	142	1176	1956	4374
	Basic Weibull (Male)	Median	0.10	1.82	6.36	173	1423	2257	4826
		2.5 th percentile	0.03	0.77	3.24	123	1059	1632	3260
		97.5 th percentile	0.28	3.68	11.5	243	2127	3493	8045
	Basic Lognormal (Female)	Median	0.63	2.49	5.23	71.1	951	1981	7871
		2.5 th percentile	0.25	1.22	2.83	47.3	569	1104	3824

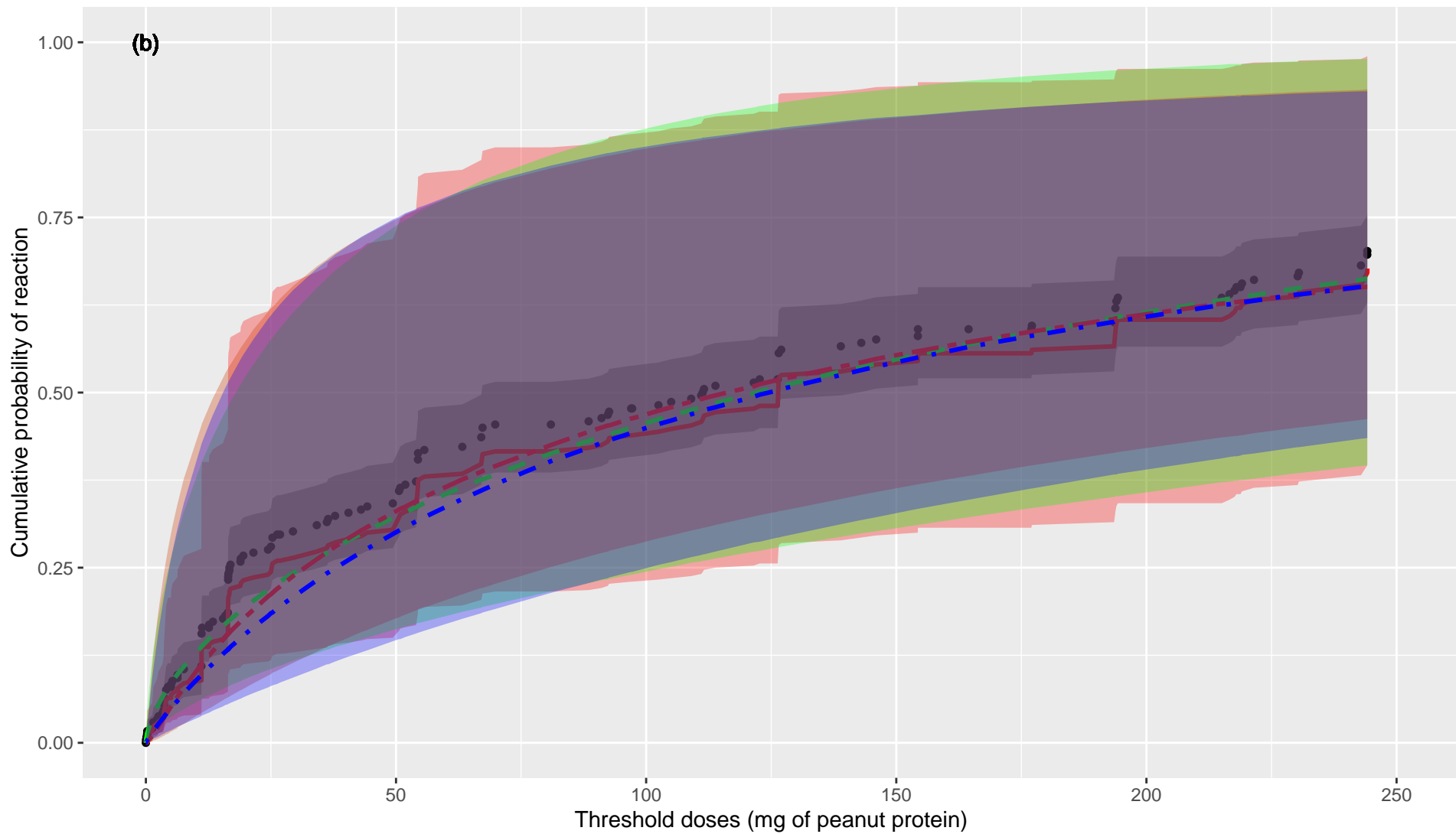
		97.5 th percentile	1.34	4.57	8.77	110.4	1834	4209	21174
	Basic Loglogistic (Male)	Median	0.81	3.60	7.93	130	2086	4575	20105
		2.5 th percentile	0.41	2.15	5.06	90.6	1281	2665	10198
		97.5 th percentile	1.54	5.87	12.1	183	3887	9396	50095
	Basic Loglogistic (Female)	Median	0.43	2.72	6.18	72.7	846	1938	12285
		2.5 th percentile	0.14	1.25	3.24	48.0	478	993	4733
		97.5 th percentile	1.06	5.20	11.0	111	1626	4253	39265
	Basic Lognormal (Male)	Median	0.40	3.24	8.38	137	2232	5712	46572
		2.5 th percentile	0.15	1.58	4.70	93.4	1335	3067	19498
		97.5 th percentile	0.91	5.73	13.6	195	4169	12061	126298






NA = Not Available. Sometimes, the bound of confidence interval for the Kaplan Meier approach cannot be estimated as Greenwood's formula, used to construct the bound of the confidence interval, does not work when the cumulative probability of reaction is close to 1.









- ◆ Kaplan Meier  95% CI
- Cox model  95% CI
- - - Weibull with covariables  95% CI
- - - Lognormal with covariables  95% CI
- · · Loglogistic with covariables  95% CI

