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Sensitivity analysis to derive a food consumption point estimate for deterministic food allergy risk assessment

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ABSTRACT

One of the input parameters in food allergy risk assessment is the amount of a given food consumed at an eating occasion. There is no consensus on how to use food consumption data when assessing the risk from unintended allergen presence in food products. A sensitivity analysis was performed to establish the optimal food consumption estimate for a deterministic food allergy risk assessment. Exposure was calculated for consumption percentiles (50th percentile, P50 to maximum) using the iFAAM consumption database in conjunction with an allergen concentration range from 1 to 1000 ppm. The resulting allergen intakes were compared to the allergic population reference doses proposed by Taylor et al. (2014) for 10 major allergenic foods. Optimal consumption percentiles were defined as those which predicted an intake below the relevant reference dose and met the defined acceptable risk level confirmed by probabilistic risk assessments. Analysis showed that, for 99% of the food groups, the P50 consumption met our criteria, while the P75 did so for 100% of the food groups. We suggest that the P75 is the optimal point estimate for use in deterministic food allergy risk assessment. It meets the safety objective and is adequately conservative for a public health context.

1. Introduction

IgE-mediated food allergy is an immune system mediated reaction that occurs rapidly after eating allergenic proteins. This can lead to a variety of symptoms in the skin, respiratory, gastro-intestinal and/or cardiovascular system. Symptoms can be mild, such as itching in the mouth or skin, hives, eczema to more severe reactions as diarrhoea, vomiting and even life-threatening reactions. Food-allergic individuals must adhere to specific avoidance diets to prevent the occurrence of allergic reactions (Sicherer and Sampson, 2018).

Ingredients in a food product must be declared in the list of ingredients, in particular regulated allergenic constituents. The most common allergenic foods for labelling are peanuts, tree nuts, milk, eggs, sesame, fish, crustaceans, molluscs, soy, and wheat or cereals containing gluten, as well as ingredients derived from those foods (Allen and Taylor, 2018). However, food production carries the potential for unintended allergen presence (UAP), through unavoidable cross-contact. UAP poses a risk for the food allergic population (Blom et al., 2018; Michelsen-Huisman et al., 2018; Sheth et al., 2010; Versluis et al., 2015). Allergen presence is also a regular cause of food recalls with considerable costs (Bucchini et al., 2016; Gupta et al., 2017). Until now, risk managers in public health authorities and industry have found assessing the public health impact of amounts of unintentionally present allergens very challenging, due to a lack of quantitative safety standard.

Food allergen risk assessment can be conducted using different methods (Madsen et al., 2009) but the general principles of risk assessment are applied for all approaches; the exposure to allergenic

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Abbreviations

ED01	eliciting dose
iFAAM	integrated approaches to food allergen and allergy management
LCI	Lower Confidence Interval
MED	minimum eliciting doses
P50, P55	the 50% Percentile of …, the 55% Percentile of food consumption distribution
RA	risk assessment
UAP	unintended allergen presence

material is compared to the hazard associated with the allergenic food. The exposure assessment includes the amount of the food consumed in which (unintended) allergenic material is present and the concentration of the (unintended) allergenic material present in the particular food product. The hazard for the food allergic population is the ability and potency of the allergenic material to elicit allergic reactions in the relevant allergic population. The hazard can be described quantitatively by the distribution of the Minimum Eliciting Doses (MED) for allergic reactions in the allergic population or certain ED percentile values of these distributions (Allen et al., 2014; Taylor et al., 2014). Probabilistic risk assessment is also currently seen as the best and most accurate approach for population risk management purposes in food allergy as it has the advantage that all available quantitative information is taken into account to link allergen concentrations in food products to the risk of a reaction for the respective allergic population (Madsen et al., 2009). However, the disadvantage of probabilistic risk assessment is that, in order to provide this accurate answer, expert knowledge (including for instance detailed background information on food consumption, the distribution of MEDs in the allergic population, sophisticated statistical programs) is necessary and therefore the method is not widely available for day to day practice of food allergen risk assessment and management in food businesses or authorities. In deterministic food allergen risk assessment, point estimates for each parameter can be utilized for a simpler, more accessible approach to risk assessment. To establish the exposure to allergens in food products in a deterministic quantitative allergen risk assessment, point estimates for food consumption at single eating occasions are needed as allergic reactions occur rapidly after eating an allergenic protein. In the present paper, we describe sensitivity analyses performed to establish the optimal percentile of the food consumption distribution to be used as a point estimate in deterministic food allergen risk assessments. This food consumption percentile should meet the predefined safety objective, yet be adequately conservative from a public health perspective. In our analyses we used the food safety objective of protecting 97–99% of the food allergic consumers, as was also done in the elaboration of reference doses by Allen et al., (2014) and Taylor et al., (2014).

2. Methods

A sensitivity analysis was done to establish the optimal percentile for food consumption for all food groups on a single eating occasion to meet the defined food safety objective. We performed it by comparing the effect of different food consumption percentiles on the outcome of the overall risk assessment. Two risk assessment frameworks were utilized, comprising a deterministic risk assessment and a more sophisticated probabilistic risk assessment (Fig. 1 and paragraph 2.4). A range of food consumption percentiles and concentrations were used as input for deterministic risk assessment, and the outcomes compared to a defined risk level of the probabilistic risk assessment. This allows us to verify that consumption percentiles do not lead to under- or over-estimation of the predefined risk level. The underlying data are the same for both risk assessments, though deterministic risk assessment uses point estimates and the probabilistic risk assessment utilizes entire data distributions.

2.1. Food consumption data

The combined food consumption database developed in the EU project iFAAM was used for the analysis. This database merges food consumption data from National Food Consumption Surveys of Denmark, France and the Netherlands into single iFAAM food consumption groups for food allergen risk assessment (Birot et al., 2018). Briefly, the food consumption data of the amount eaten per eating occasion for food products was created per country and food products with similar food consumption were grouped using verification by probabilistic risk assessment. Products with a relevant risk difference were placed in subgroups. This food consumption database provided the food consumption distribution for each of the food groups for the consumption amount (kilogram food) per eating occasion. The total food consumption distribution was used for the probabilistic risk assessment, whereas the percentiles (the P50, P55, …up to P100) of the food consumption distribution for each food group were used as input values for consumption in the deterministic risk assessment sensitivity analysis.

2.2. Food contamination data

For the deterministic approach and for the probabilistic approach, the sensitivity analyses were performed using allergen concentrations in the food products ranging from 1 to 1000 ppm (1, 3, 10, 30, 100, 300, 600 or 1000 mg protein of the allergenic source/kg food products) These levels are typical concentrations found as the levels of UAP in food products in many published surveys (summarized in Allen and Taylor, 2018) and were chosen to cover a wide range of concentrations and to ensure that the allergenic protein intakes in the various food groups would be both below and above reference doses.

2.3. Threshold doses in the food allergic population

Taylor et al., (2014) derived reference doses for several major food allergens from the dose distribution modelling of a large dataset of individual MED from bibliographic data and unpublished clinical data. In the present study, for the probabilistic risk assessment, we used these threshold dose (MED) distributions. For each allergenic food, probability distributions (Weibull, Log Normal and Log Logistic) were fitted to the individual discrete or cumulative 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) and R Survival Package (R v2.13.0 or higher) as described previously (Taylor et al. 2009, 2014). For most allergens (egg, hazelnut, lupin, mustard, sesame, shrimp, soy, wheat) three parametric models are applied (Weibull, Log Normal and Log Logistic). For milk and peanut the Weibull distribution did not meet the criteria for defining the reference doses and only the LogNormal and LogLogistic distributions were used (see Taylor et al., 2014).

For the deterministic risk assessment and the accompanying sensitivity analyses, we used reference doses (in mg protein of allergenic food) that are derived from the same data set and dose response modelling as described above. These doses were based on the ED01 or the lower confidence limits of the ED05 of the dose distribution models, and protect between 97% and 99% of the food allergic population according to the most conservative estimate from dose-distribution models (Taylor et al., 2014; Allen et al., 2014).

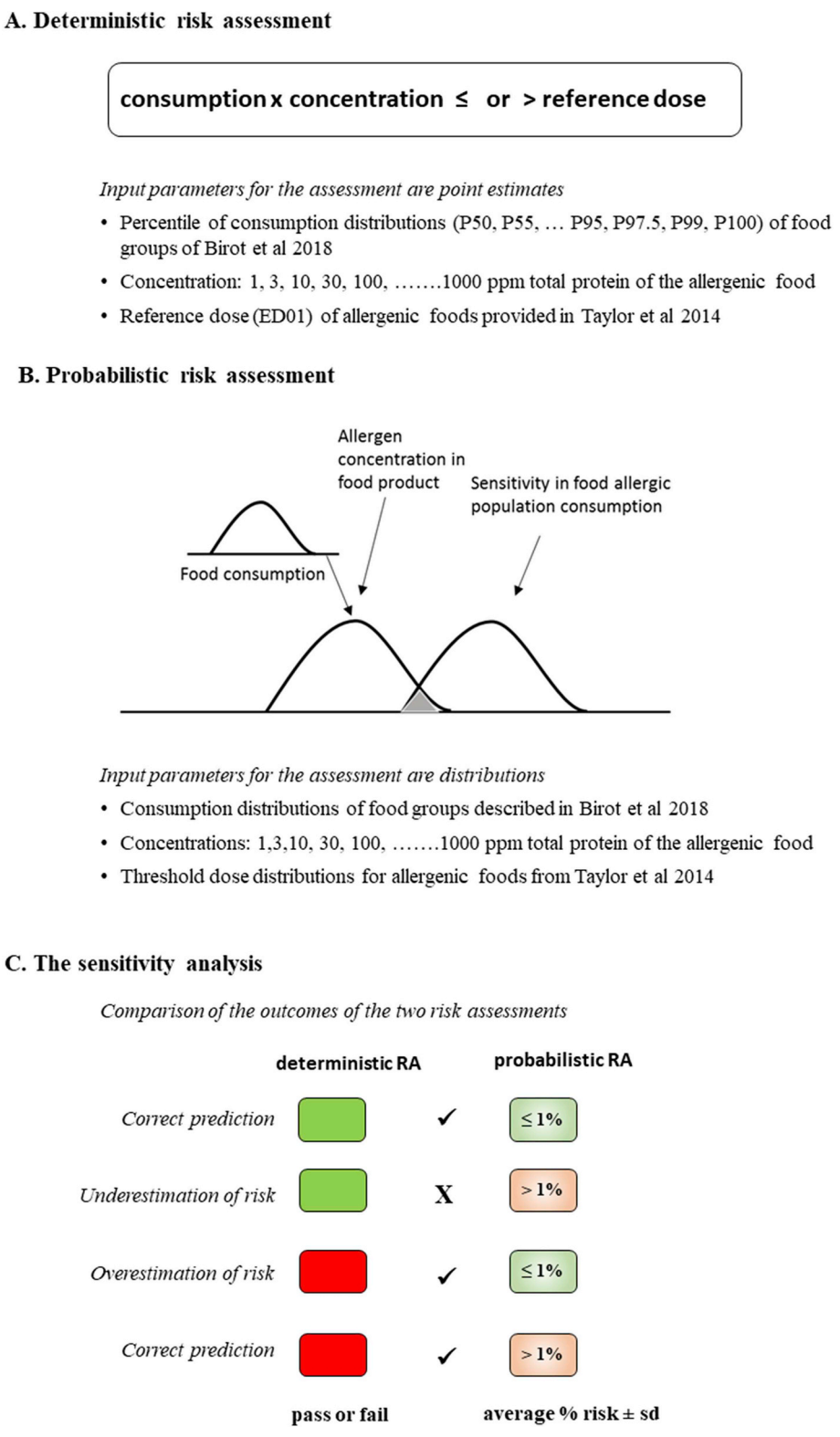

Fig. 1. Description of the sensitivity analysis to derive an optimal point estimate for allergen risk assessment. The deterministic RA (A) and the probabilistic RA (B) outcomes are compared in a sensitivity analysis (C). A) The formula and the input parameters for the deterministic RA (see details in the Material and Method section). The outcome is a binary answer: if the amount of allergenic protein in the amount consumed is at or below the relevant reference dose, a product is considered to "pass", and the allergy risk not to require further mitigation (green box in C). Conversely, if it exceeds that amount, the product "fails" (red box in C). B) Schematic description of the probabilistic RA (details are in the Material and Methods section) using the distributions of the same datasets as in A). The cut off for probabilistic RA is the estimated allergic responders is either at or below (light green box in C) or it is above (light red box) the defined risk level at the reference dose for each of the allergens and parametric models and indicated here for simplicity as ≤ 1% and > 1% (see Table 1 for the % risk for each parametric model). C) In the sensitivity analysis the outcomes of the two risk assessments are compared. Underestimation or overestimation of the risk by the deterministic RA occurs if too low or too high food consumption percentiles were used in the deterministic modelling. The comparison with the more sophisticated probabilistic modelling is thus used in the sensitivity analyses to derive the optimal food consumption percentile for deterministic RA. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

2.4. Risk assessment

2.4.1. Deterministic risk assessment

The deterministic allergen risk assessment is captured in the following formula:

Intake [Consumption (kg food) X concentration (mg protein of allergenic food/kg food)] ≤ or > Reference Dose (mg total protein of allergenic source)

Point estimates based on the total available information are required for each of the input parameters. For consumption, percentiles of the food consumption distribution for food groups were used as described in section 2.1. For contamination, the different concentration levels presented in section 2.2 were used. The intake is calculated by multiplying the amount of food consumed by the concentration of allergenic food. This intake dose was then compared with the reference

Table 1
The percentage allergic responders estimated at the reference dose per parametric model for major allergenic foods.

Reference dose (mg protein)	Peanut	Milk	Egg	Hazelnut	Soy Flour	Wheat	Lupin	Sesame	Shrimp	Mustard
	0.2 mg	0.1 mg	0.03 mg	0.1 mg	1 mg	1 mg	4 mg	0.2 mg	10 mg	0.05 mg
Distribution[a]	% allergic responders (confidence interval)									
LogLogistic (%)	1.4 (1, 1.8)	0.8 (0.5, 1.3)	1.2 (0.6, 2.1)	0.6 (0.3, 1.2)	1.1 (0.2, 3.1)	1.5 (0.2, 4.3)	1.1 (0.04, 4.6)	0.6 (0.02, 2.9)	1.3 (0.13, 3.88)	0.9 (0.07, 3.4)
LogNormal (%)	0.7 (0.5, 1.1)	0.3 (0.1, 0.5)	0.6 (0.2, 1.3)	0.2 (0.06, 0.6)	0.3 (0.01, 1.7)	0.9 (0.05, 3.7)	0.4 (0.01, 3.1)	0.2 (0.01, 2.2)	1.5 (0.11, 4.6)	0.4 (0.01, 2.6)
Weibull (%)			2.3 (1.2, 3.6)	1.6 (0.8, 2.7)	2.7 (0.7, 6.2)	3.3 (0.8, 7.6)	3.1 (0.3, 9.0)	1.4 (0.08, 5.2)	1.6 (0.2, 4.5)	1.6 (0.2, 4.9)

[a] For each parametric model threshold distribution, the ED in % allergic responders at the reference dose is provided including the confidence interval. Note: for peanut and milk the Weibull distribution was not fitting the data and was therefore omitted in derivation of the reference dose (Taylor et al., 2014).

doses proposed by Taylor et al. as described in section 2.3 (Taylor et al., 2014). The reference doses in Taylor et al. (2014) are provided in mg of total protein from the allergenic source and those concentrations were converted to mg of food using typical protein levels for those foods.

The outcome of the risk assessment is a binary answer, either the intake is at or below the reference dose or it exceeds the reference dose (see also Fig. 1C). A product is considered to "pass", and the allergy risk not to require further mitigation, if the amount of allergenic protein in the amount consumed is at or below the relevant reference dose. Conversely, if it exceeds that amount, the product "fails".

2.4.2. Probabilistic risk assessment

The quantitative probabilistic risk assessment is performed as described in (Kruizinga et al., 2008; Spanjersberg et al., 2007). We performed the risk assessments for allergic users of food products containing the relevant allergenic proteins, thus we set the percentage of individuals consuming the selected food products as well as the percentage of food products contaminated both at 100%. Allergen contamination was assumed to be uniformly distributed within the food. The resulting risk analysis provided an estimation of the percentage of expected allergic reactions in the allergic population eating contaminated products. The quantitative probabilistic risk assessment model includes the distribution of consumption of the allergen derived from the amount of food that is consumed (section 2.1) and the distribution of the concentration of the allergen in the food product (section 2.2). These input parameters are combined in a Monte Carlo simulation to estimate the exposure, which is compared with the population dose-distribution of MEDs presented in section 2.3.

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

2.5. Sensitivity analysis

In the sensitivity analysis, all binary outcomes of the deterministic RA are compared with the risk outcome of the probabilistic RA (see Fig. 1A, B and C). The optimal percentile for food consumption for all food groups on a single eating occasion is the percentile that results into meeting the defined food safety objective, but is not overconservative (or underestimating the risk). The (food) safety objective or defined standard for the present study is the % risk at the reference dose. Reference doses as used in the present paper were provided in Taylor et al., (2014). These reference doses were derived using the ED01 or the lower confidence interval of the ED05 of the 2 or 3 parametric threshold dose distribution models for each allergen: the LogNormal, LogLogistic and Weibull (Weibull was excluded for peanut and milk) (see Taylor et al., 2014 and paragraph 2.3). Calculating back from the reference dose to the estimated percentage risk for each parametric model, therefore results in a percentage that will vary slightly around the overall value of 1.0%. For example, the reference dose for peanut is 0.2 mg peanut protein and is based on the ED01s of the LogNormal and LogLogistic models, which are 0.3 mg and 0.13 mg, respectively. Consequently, by calculating back to the risk at 0.2 mg peanut protein for each parametric model, this risk corresponds to 0.7% for the LogNormal distribution and 1.4% for the Loglogistic distribution. For the sensitivity analysis, we therefore recalculated to the exact % predicted risk at the reference dose for each allergen and parametric model (Table 1). These percentages were used as the cut off values in the probabilistic risk assessment during the sensitivity analysis.

If the predicted proportion of reactions in the allergic population exceeds the % risk at the reference dose in probabilistic RA, the deterministic RA should also indicate that the defined risk level was exceeded, i.e. the intake assessment should be above the reference dose based on the defined risk level. Also, if the probabilistic risk assessment estimated risk for allergic responders at or below the % risk at the

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	85								
P55	90								
P60	90								
P65	100								
P70	100								
P75	100								
P80	120								
P85	131.6								
P90	150								
P95	180								
P97.5	200								
P99	250								
P100	600								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.6	1.2	2.6	5.2	11	20	28	35
LogNormal (%)	0.2	0.7	2.1	5.1	12	21	29	36
Weibull (%)	1.5	2.5	4.4	7.3	13	20	27	33

Fig. 2. Example hazelnut in *Ice cream* showing the comparison of the deterministic risk assessment with the probabilistic risk assessment for determination of the optimal percentile of the food consumption distribution. Shown is A) the deterministic risk assessment for concentrations of hazelnut in*Ice cream* (in protein of the allergenic food/product) using a range of percentiles of the food consumption distribution for ice cream (P50 − P100). And B) the estimated risk for allergic responders (in %) at the different concentrations of hazelnut protein in ice cream using probabilistic risk assessment. In case of green the estimated risk is at or below the defined risk level, in case of red this is exceeding this level. The cut off values for the different parametric models are based on the confidence interval of the estimated risk at the reference dose (see Table 1). Note that the outcome for a particular parametric model can be different, see for example at 3 ppm: the estimated risk is above the cut off value forLogNormal, whereas for the LogLogistic and Weibull the risk is just within the confidence interval. If one model predicts a risk above the cut off value the decision is that there is a risk. **The conclusion over all 3 models is that comparing the deterministic RA with the probabilistic RA, P50 − P75 are adequately predicting. At P80 and above the deterministic RA is conservative**. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

reference dose, the deterministic RA outcome should at least predict a "pass", i.e. the intake is below or at the reference dose. Because the deterministic RA should take into account the variability of the datasets used and incorporate some conservatism, it may predict that there is a risk (fail) whereas the corresponding probabilistic risk assessment will estimate a level of risk below the agreed upon safety objective (pass). The optimal percentile for food consumption for all food groups on a single eating occasion was selected after comparison of the outcomes of the deterministic risk assessment using all food consumption percentiles with the probabilistic risk assessment.

This sensitivity analysis was built into an R-shiny package of R Studio® to compare all risk assessment outcomes of the deterministic risk assessment with the probabilistic risk assessment.

3. Results

In total 1344 deterministic risk assessments were done with all percentiles and for all food groups risk assessments. The outcomes of each of these was compared with the probabilistic RA outcomes. For explanatory purposes, results are described in more detail here for two cases: hazelnut in *Ice cream* (Fig. 2) and peanut in *Spices and salts* (Fig. 3) In Supplement S1 additional examples for several other allergen and food group combinations are presented (wheat and shrimp in *Spices and salts*, shrimp in *Composite dish*, peanut in *Sauces and condiments* and milk in *Cheese*) are presented. Note that food groups contain multiple food items, including foods derived from different sources. The food group *Cheese* thus contains also cheeses made from other sources than cow's milk, such as goat milk. The overall analysis is presented in paragraph 3.2.

3.1. Examples of the sensitivity analysis

3.1.1. Example of hazelnut in ice cream

The deterministic risk assessment outcomes for the food group *Ice cream* contaminated with different concentrations of hazelnut are shown in Fig. 2A. The binary outcome predicts either that there is risk above (red) or at or below the intended risk level (green). Fig. 2B also provides the risk estimated by the probabilistic risk assessment at the bottom of the figure. For each concentration of hazelnut protein in the ice cream, the % predicted allergic reactions in the hazelnut-allergic population is estimated and the conclusion whether it is at or below the risk level (green) or exceeds the risk level (red) at the reference dose for the 3 parametric models for the threshold distribution is given (as indicated in Table 1).

Next the lowest percentile of food consumption is identified that produces a deterministic RA outcome in compliance with the predefined risk level (equal to or less than the % allergic responders at the reference dose). In the particular example of Fig. 2, the estimated risk at 1 ppm hazelnut protein per kg ice cream is below the pre-defined risk level for all 3 parametric models. At 3 ppm the probabilistic RA

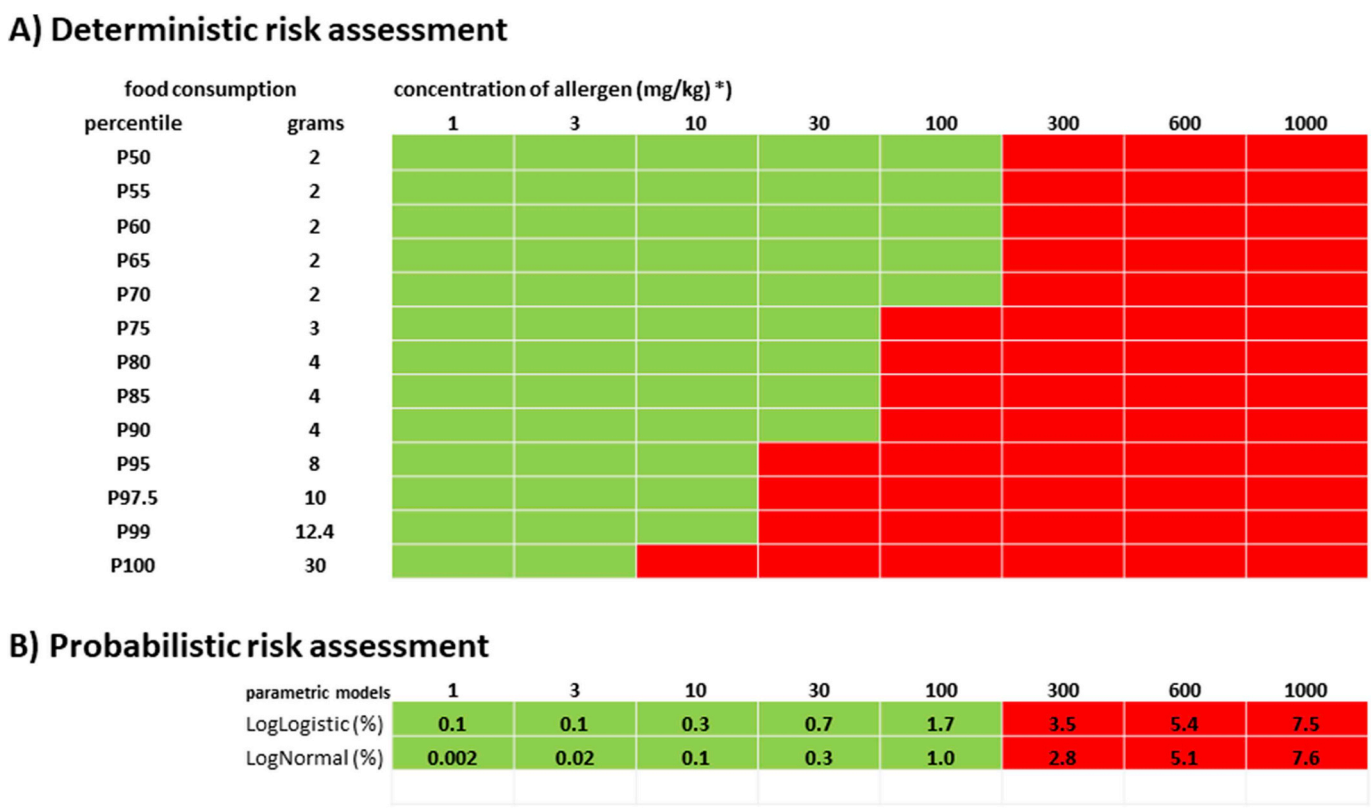

Fig. 3. Example *peanut in Spices and salts* for determination of the optimal percentile of the food consumption distribution. Shown is A) the deterministic risk assessment for concentrations of peanut in *spices and salt* (in protein of the allergenic food/product) using a range of percentiles of the food consumption distribution for spices and salt (P50 − P100). And B) the estimated risk for allergic responders (in %) at the different concentrations of peanut protein in *spices and salt* using probabilistic risk assessment. In case of green the estimated risk is at or below the defined risk level, in case of red this is exceeding this level. The cut off values for the different parametric models are based on the confidence interval of the estimated risk at the reference dose (see Table 1). Note that for peanut only the LogLogistic and LogNormal distributions are taken into account as the Weibull distribution does not meet the criteria for elaboration of the reference dose (Taylor et al., 2014). **The conclusion over the 2 models is that comparing the deterministic RA with the probabilistic RA, P50 − P70 are adequately predicting. At P75 and above the deterministic RA is conservative.** (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

estimated a risk above the cut off values for 1 of the 3 parametric models, and the conclusion is that the product "fails" the risk assessment according to the pre-defined criteria. The deterministic risk assessment predicted this conclusion correctly for all percentiles at 3 ppm, whereas at 1 ppm the prediction was in agreement for the P50 to P75 of the food consumption distribution. Using the consumption values of P80 to P100 of the distribution combined with 1 ppm, the deterministic risk assessment was more conservative and predicts a risk above the pre-defined benchmark, whereas the probabilistic modelling estimated a risk that was below the agreed risk level. The conclusion in this example is that using any percentile between P50 and P75 for deterministic risk assessments of ice cream consumption adequately predicts risk outcomes in agreement with probabilistic risk assessment results; additionally, incorporating the P80 or higher the risk assessment scenario would exceed the pre-defined degree of protection.

3.1.2. Example of peanut in spices and salt

The RA outcomes for peanut in food group *Spices and salts* are presented in Fig. 3. The lowest percentile of food consumption that provides a deterministic RA outcome in compliance with the predefined risk level (equal to or less than the % allergic responders at the reference dose) is identified. At 100 ppm peanut in *Spices and salt*, the estimated risk in the probabilistic approach is below the pre-defined risk level for both parametric models. For the deterministic risk assessment the prediction is in agreement for the P50 to P70 of the food consumption distribution, from P75 or higher the risk assessment is more conservative and would exceed the pre-defined degree of protection. The conclusion in this example is that using any percentile between P50 and P70 for deterministic risk assessments of peanut in *Spices and salts* consumption adequately predicts risk outcomes in agreement with probabilistic risk assessment results.

Table 2
The percentage product and allergen combinations at each percentile of the food distribution for which the deterministic RA outcome is in compliance with the probabilistic RA.[a]

Percentile of food consumption in deterministic RA	% food groups and allergen combinations in compliance with the probabilistic RA			
	Log Logistic	LogNormal	Weibull	Overall
P50	99.4%	99.2%	100%	99.5%
P55	99.8%	99.6%	100%	99.8%
P60	100%	99.6%	100%	99.8%
P65	100%	99.8%	100%	99.9%
P70	100%	99.8%	100%	99.9%
P75	100%	100%	100%	100%
P80	100%	100%	100%	100%
P85	100%	100%	100%	100%
P90	100%	100%	100%	100%
P95	100%	100%	100%	100%

[a] For most allergens 3 parametric models are used, except for milk and peanut in which the Weibull distribution did not meet the criteria as presented in (Taylor et al., 2014).

3.2. Overall analyses over all food groups and intake scenarios

The procedure was repeated for all food groups and allergens (480 combinations) and parametric models, and in total 1344 risk assessments were performed. Table 2 shows the percentage (%) of scenarios and combinations that were predicted correctly at each percentile for each of the parametric models. These data demonstrate that using the P50 of food consumption for almost all food groups (99.5%) provided a deterministic RA outcome in accordance with probabilistic RA results (Table 2). A few combinations required a higher food consumption percentile (see also Table 3) and when the P75 point estimate for consumption was used, all the scenarios and combinations provided deterministic RA results that agreed with the probabilistic RA outcomes (Table 2). Table 3 illustrates the combinations in which the deterministic RA required a consumption estimate utilizing a percentile above the P50 for correct risk predictions (see also Supplemental Fig. S1 examples D, E and F). The predicted probabilities of allergic reactions in the scenarios presented in Table 3 were just outside the ED01 estimated risk confidence intervals for milk or peanut and thus a higher point estimate than the P50 was needed (i.e. P55—P75). The overall conclusion is that the P75 is a safe, conservative point estimate to choose for a consumption value to be used in a simple, quick deterministic RA.

4. Discussion

As part of a global allergen management system, it is crucial to have one cohesive, agreed quantitative risk assessment approach. In the EU project iFAAM, a tiered risk assessment approach was developed to enable the systematic evaluation of allergen risks pertaining to a production line, process or factory (Summarized in the final report of the project (IFAAM, Project coordinator C. Mills, 2018)). In this framework, a deterministic risk assessment provides an initial quantitative test, offering a binary answer to the user: either the risk from unintended allergen presence is at or below the agreed safety objective, or it is above. The initial test was developed for easy application by food business operators regardless of size and without specific expertise in food allergen risk assessment. Of the three main parameters utilized in allergen risk assessments, the amount of a food product consumed (per eating occasion) and the distribution of minimum eliciting doses (MEDs) in the food-allergic population are components that are not readily available and accessible to the typical food business operator. Taylor and colleagues (Taylor et al., 2014) previously proposed reference doses based on distribution modelling of MEDs in the food allergic population aimed protecting 97–99% of allergic individuals against mild objective reactions. Adoption of these reference doses as benchmarks for allergen management is growing (Yeung and Robert, 2018; Waiblinger and Schulze, 2018; Scicom Wetenschappelijk Comite van het Federaal Agentschap voor de Veiligheid van de Voedselketen, 2017; Sjögren Bolin, 2015; Danish Veterinary and Food Administration, 2018) and indeed form a key element of schemes such as the Voluntary Incidental Trace Allergen Labelling (VITAL) program. This is guidance for allergen management developed by the Allergen Bureau of Australia and New Zealand which provides a quantitative basis for precautionary allergen labelling of food products ((Brooke-Taylor et al., 2018) and http://allergenbureau.net/vital/). However, the lack of a good evidence-based foundation for the food consumption parameter is a source of substantial confusion among those performing the risk assessment including more experienced risk assessors when choosing the value(s) for a risk assessment. A diverse range of inputs is seen in practice, for example both the nominal portion size or daily consumption amounts are derived for nutritional purposes and either underestimate (portion size) or over-estimate (daily consumption) exposure (Madsen et al., 2014). Users also tend to select the maximum consumption amounts (P97.5, P99, Pmax) to be “on the safe side” and therefore could overestimate the risk (personal experience in workshops with risk managers/QA managers of food business). These diverse formulations of consumption amounts lead to highly divergent quantitative risk estimates. We therefore performed an extensive sensitivity analysis of the consumption parameter to derive the optimal food consumption point estimate for an easy to use, deterministic allergen risk assessment. Our selected food safety objective in deriving this single value to cover all food groups was that the risk outcome (% predicted reactions) of the deterministic risk assessment must never exceed the risk outcome predicted at the reference dose for the relevant allergen, calculated using probabilistic risk assessment. The sensitivity analysis approach was developed around food groups and can be applied to different food consumption databases. In this study we demonstrated that the P75 of the food consumption distributions of the iFAAM database, based on food consumption from Denmark, France and The Netherlands, meets the agreed safety objective for allergen risk assessment. Our approach is based on a fairly narrow range of databases, even in a European context. In order to develop more globally applicable consumption reference amounts for food products, other national food consumption databases must become available for allergen risk assessment and be analysed with similar approaches. Future studies need to broaden their scope to include not only other Western dietary surveys (US, Canada, Australia, etc), but also Asian dietary surveys (China, Japan, etc), and others. Subpopulations such as infants, children, teenagers and adults could also be analysed for possible differences when data are available. Of note, current allergen risk assessments are performed using food consumption data from the general population and it is therefore assumed that consumption of any food group by the food-allergic population mirrors that of the general population, when consumption occurs. To substantiate this assumption, the MIRABEL project attempted to collect dietary survey data from the peanut-allergic and general populations. Due to low participation rates in the general population, a

Table 3
The food group and allergen combinations requiring a percentile for deterministic RA above P50 for compliance with probabilistic RA.

Food group	allergen	Probabilistic risk assessment			deterministic RA
			% risk[a]	cut off value at reference dose	required percentile
cheese	milk	LN	0.69%	0.3 (0.1, 0.5)	P55
	milk	LL	1.32%	0.8 (0.5, 1.3)	P55
supplement	milk	LN	0.61%	0.3 (0.1, 0.5)	P75
chocolates	peanut	LN	1.52%	0.7 (0.5, 1.1)	P55
	peanut	LL	2.16%	1.4 (1, 1.8)	P55
Sauces used as condiments and dessert sauces	peanut	LN	1.52%	0.7 (0.5, 1.1)	P65
	peanut	LL	2.18%	1.4 (1, 1.8)	P65

[a] The risk for allergic reactions (in %) estimated with probabilistic RA for the particular food group and allergen combinations at the LogNormal distribution (LN) and LogLogistic (LL) distribution. The risk for all other products (n = 473 out of 480) is within the confidence interval of the risk estimate at the reference dose.

full comparative analysis could not be performed. However, it was observed that tree nut allergy and anxiety-related factors modulate food consumption behaviour in peanut-allergic patients (Crépet et al., 2015; Papadopoulos et al., 2018). In the Netherlands TNO, together with University Medical Center Utrecht and the National Institute for Public Health and the Environment have recently started a food consumption survey among the food-allergic population with a survey and study group matching the general population in another effort to substantiate the assumption that consumption amounts are similar between the food-allergic and general populations (manuscript in preparation).

Another possible future research area includes reviewing the food safety objective, which was selected as 97–99% of the allergic population for the present study by definition of the reference dose in Taylor et al., (2014). This applies particularly in the light of new experimental clinical approaches which permit a better characterization of the risk, such as the single dose challenge study (Hourihane et al., 2017). In the future, a different safety objective may be judged more appropriate, for example ED05 values for the allergic population may be chosen, or the data for the dose-response distributions could be supplemented with more data resulting in updated reference doses. Due to the fit-for-purpose combination of risk management decision (ED01) and consumption point estimate calculation, the approach for the consumption point estimate sensitivity analysis would need to be reapplied if another safety objective were chosen. As illustration, the food group and allergen combinations of Table 3 with a safety objective of an ED05 would lead to P50 point estimates being appropriate for all food groups (Supplement S2).

The current analysis demonstrates that the median (P50) of food consumption already meets the agreed level of protection for a substantial number of food groups and only a few food group/allergen combinations require a higher point estimate of consumption. With the P75 percentile, the predicted risk outcome is similar to the probabilistic risk assessment outcome for all food groups. Using an additional level of conservatism in allergen risk assessment, for example as generally applied within toxicology, would mean selection of the highest percentiles of food consumption, a P95, P97.5 or even the maximum food consumption and would ignore the agreed aimed level of protection for allergen risk assessments. Also, it would likely result in most, if not all deterministic allergen risk assessments “failing”; leading to unnecessary allergen management measures and a likely increase in precautionary allergen labelling, exacerbating existing issues and thereby failing to benefit the allergic consumer, and possibly continuing to harm them. In addition the overestimation of risk could lead to discarding of the products and needless waste of food. Furthermore, the conservatism applied in general toxicological risk assessments arises in large part from the uncertainties inherent in extrapolating hazard data from animal studies towards humans. These uncertainties are largely absent when using data from food allergic individual challenge studies, which take place in the population of interest. Furthermore, the probabilistic risk assessment performed in the present paper involved some conservatism since all products (100%) were defined to be contaminated with the allergen and all consumers of the product were defined to be food allergic (100%). Thus, it was concluded that the P75 is the optimal point estimate for use in deterministic allergen risk assessment for a balance between conservatism and meeting the agreed safety objective.

Finally, though apart from the sensitivity analyses presented here in the present paper, the result of a food allergen risk assessment is also determined by the other variables (i.e. the concentration of the allergen in the food and the threshold dose distribution of the food allergic population). A major uncertainty in the risk assessment will be present in the analytical determination of the concentration (Baumert, 2014; Walker et al., 2016). This concentration of unintentionally present allergen in a food product is an important component in the risk assessment and will be provided by the food manufacturer. Often this contamination value will be the allergen concentration derived from analyses of product or ingredient samples or of intermediate steps. This part will very likely have the largest uncertainty and variation, caused by factors such as product sampling, sample preparation, extraction methods, analytical kits used. Further recommendations and guidance for determination of the concentration of allergen for input to the risk assessment could be beneficial for all stakeholders.

5. Conclusion

In conclusion, the present paper shows that the 75th percentile of the food consumption distribution per eating occasion is the optimal point estimate for use in deterministic allergen risk assessment meeting the safety objective of protecting 97–99% of allergic individuals from objective allergic reactions to unintended allergen presence.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2019.01.025.

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Supplement S1 Several examples additional to the publication figures 2 and 3.

Six examples additional to the publication Figures 2 and 3 showing the comparison of the deterministic risk assessment with the probabilistic risk assessment and the overall conclusion for the specific food group and allergen combination.

Example S1-A Example wheat in food group *Spices and salts*

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	2								
P55	2								
P60	2								
P65	2								
P70	2								
P75	3								
P80	4								
P85	4								
P90	4								
P95	8								
P97.5	10								
P99	12.4								
P100	30								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.01	0.02	0.05	0.1	0.4	1.1	2.1	3.2
LogNormal (%)	0	0	0.004	0.02	0.1	0.7	1.6	2.9
Weibull (%)	0.1	0.2	0.4	0.7	1.4	2.8	4.2	5.7

Conclusion over all 3 parametric models : Comparing deterministic RA with the probabilistic RA, P50 – P75 are adequately predicting. At P80 and above the deterministic risk assessment is conservative.

Example S1-B Example shrimp in food group *Spices and salts*

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	2								
P55	2								
P60	2								
P65	2								
P70	2								
P75	3								
P80	4								
P85	4								
P90	4								
P95	8								
P97.5	10								
P99	12.4								
P100	30								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.01	0.02	0.05	0.09	0.2	0.3	0.5	0.6
LogNormal (%)	0.001	0.002	0.01	0.03	0.1	0.2	0.4	0.6
Weibull (%)	0.03	0.05	0.08	0.1	0.3	0.5	0.7	0.8

Conclusion over all 3 parametric models : Comparing deterministic RA with the probabilistic RA, P50 – P100 are adequately predicting. At P99 and above the deterministic risk assessment is conservative.

Supplement S1 Examples – Continued

Example S1-C Example shrimp in food group *Composite dish*

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	200								
P55	225								
P60	237								
P65	240								
P70	291								
P75	320								
P80	338								
P85	380								
P90	450								
P95	500								
P97.5	650								
P99	750								
P100	1500								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.2	0.3	0.7	1.3	2.4	4.3	6.1	8.0
LogNormal (%)	0.1	0.3	0.7	1.5	3.1	5.8	8.3	11
Weibull (%)	0.3	0.5	0.9	1.6	2.8	4.7	6.5	8.3

Conclusion over all 3 parametric models: Comparing deterministic RA with the probabilistic RA, P50- P100 is adequately predicting.

Example S1-D Example peanut in food group *Sauces and condiments*

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	16								
P55	19.4								
P60	20								
P65	23.3								
P70	26								
P75	30								
P80	32								
P85	36								
P90	46.5								
P95	60								
P97.5	75								
P99	97.1								
P100	500.1								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.5	1.0	2.2	4.5	9.5	18	25	32
LogNormal (%)	0.1	0.5	1.5	4.0	9.9	19	27	34
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P65 – P100 are adequately predicting.

Supplement S1 Examples – Continued

Example S1-E Example milk in food group *Cheese*. Note that this food group can contain cheeses made from other sources than cow's milk, such as goat milk.

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	32								
P55	35								
P60	40								
P65	40								
P70	44								
P75	48								
P80	59.4								
P85	60								
P90	80								
P95	90								
P97.5	100								
P99	150								
P100	1000								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.6	1.3	2.9	5.7	12	21	29	36
LogNormal (%)	0.2	0.7	2.2	5.4	13	23	32	39
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P55 – P100 are adequately predicting.

Example S1-F Example milk in food group *Supplement*

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	1								
P55	1								
P60	1								
P65	1								
P70	1								
P75	2								
P80	2								
P85	2								
P90	3								
P95	4								
P97.5	6								
P99	10								
P100	60								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.1	0.1	0.2	0.5	1.2	2.5	3.8	5.3
LogNormal (%)	0.0	0.0	0.0	0.2	0.6	1.8	3.2	4.8
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P75 –P100 are adequately predicting.

Supplement S2 An analysis at the ED05

Supplemental Table S2-1 to the manuscript shows those food group and allergen combinations requiring a percentile for deterministic risk assessment above P50 for compliance with probabilistic risk assessment when the safety objective is the reference dose (part of table 3 in the manuscript). The last column present the point estimates required when the ED05 of the threshold dose distributions is the safety objective. In this situation the agreed safety level for the deterministic risk assessment is 1.5 mg peanut protein or milk protein (Table S2-2).

Supplemental Table S2-1 The percentile required when the safety objective is the ED05 for the food group and allergen combinations of table 3 in the manuscript.

			required percentile in deterministic RA in case the safety objective is the	
Food group	**allergen**		**reference dose of Taylor et al 2014**	***ED05***
cheese	milk	LN	P55	*P50*
	milk	LL	P55	*P50*
supplement	milk	LN	P75	*P50*
chocolates	peanut	LN	P55	*P50*
	peanut	LL	P55	*P50*
Sauces used as condiments and dessert sauces	peanut	LN	P65	*P50*
	peanut	LL	P65	*P50*

*) the risk for allergic reactions (in %) estimated with probabilistic RA for the particular food group and allergen combinations at the LogNormal distribution (LN) and LogLogistic (LL) distribution.

Supplemental Table S2-2 The cut off values for the % allergic responders in the probabilistic risk assessment when the safety objective is at a dose of 1.5 mg peanut protein or milk protein (related to the ED05 of the peanut or milk threshold distribution).

Distribution	**peanut**	**milk**
lognormal	4.9 % (4.2-6.2)	4.1 % (2.6-6.0)
loglogistic	5.3 % (4.2-6.5)	4.7 % (3.2-6.2)

Presented below are 2 examples from Table S2 to illustrate how this new safety objective affects the analysis to determine the percentile of food consumption deterministic risk assessment and the probabilistic risk assessment outcome.

Example peanut in Sauces and condiments

Reference dose ED01

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	16								
P55	19.4								
P60	20								
P65	23.3								
P70	26								
P75	30								
P80	32								
P85	36								
P90	46.5								
P95	60								
P97.5	75								
P99	97.1								
P100	500.1								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.5	1.0	2.2	4.5	9.5	18	25	32
LogNormal (%)	0.1	0.5	1.5	4.0	9.9	19	27	34
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P65 – P100 are adequately predicting.

Example peanut in Sauces and condiments

Reference dose ED05 1.5 mg

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	16								
P55	19.4								
P60	20								
P65	23.3								
P70	26								
P75	30								
P80	32								
P85	36								
P90	46.5								
P95	60								
P97.5	75								
P99	97.1								
P100	500.1								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.5	1.0	2.2	4.5	9.5	18	25	32
LogNormal (%)	0.1	0.5	1.5	4.0	9.9	19	27	34
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P50 onwards is adequately predicting.

So for the ED01 a P65 was adequate. For the ED05 the P50

Blom et al (2019) Supplement S2 to *Sensitivity analysis to derive a food consumption point estimate for deterministic food allergy risk assessment*

Example milk in Cheese

Reference dose ED01

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	32								
P55	35								
P60	40								
P65	40								
P70	44								
P75	48								
P80	59.4								
P85	60								
P90	80								
P95	90								
P97.5	100								
P99	150								
P100	1000								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.6	1.3	2.9	5.7	12.0	21.0	29.0	36.0
LogNormal (%)	0.2	0.7	2.2	5.4	13.0	23.0	32.0	39.0
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P55 –P100 are adequately predicting.

Example milk in Cheese

Reference dose ED05 1.5 mg

A) Deterministic risk assessment

food consumption		concentration of allergen (mg/kg) *)							
percentile	grams	1	3	10	30	100	300	600	1000
P50	32								
P55	35								
P60	40								
P65	40								
P70	44								
P75	48								
P80	59.4								
P85	60								
P90	80								
P95	90								
P97.5	100								
P99	150								
P100	1000								

B) Probabilistic risk assessment

parametric models	1	3	10	30	100	300	600	1000
LogLogistic (%)	0.6	1.3	2.9	5.7	12.0	21.0	29.0	36.0
LogNormal (%)	0.2	0.7	2.2	5.4	13.0	23.0	32.0	39.0
Weibull (%)								

Conclusion over all 2 parametric models : Comparing deterministic RA with the probabilistic RA, P50 –P100 are adequately predicting. (P80-P100 are conservative).

So for the ED01 a P55 was adequate. For the ED05 the P50 is adequate