Food and Chemical Toxicology 146 (2020) 111831

Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

Full range of population Eliciting Dose values for 14 priority allergenic foods and recommendations for use in risk characterization

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ARTICLE INFO

Keywords:
Food allergy
Food allergen
Allergenic food
Eliciting dose
Risk assessment
Risk management

ABSTRACT

Previously, we published selected Eliciting Dose (ED) values (i.e. ED01 and ED05 values) for 14 allergenic foods, predicted to elicit objective allergic symptoms in 1% and 5%, respectively, of the allergic population (Remington et al., 2020). These ED01 and ED05 values were specifically presented and discussed in the context of establishing Reference Doses for allergen management and the calculation of Action Levels for Precautionary Allergen Labeling (PAL). In the current paper, we publish the full range of ED values for these allergenic foods and provide recommendations for their use, specifically in the context of characterizing risks of concentrations of (unintended) allergenic proteins in food products.

The data provided in this publication give risk assessors access to full population ED distribution information for 14 priority allergenic foods, based on the largest threshold database worldwide. The ED distributions were established using broad international consensus regarding suitable datapoints and methods for establishing individual patient's NOAELs and LOAELs and state of the art statistical modelling. Access to these ED data enables risk assessors to use this information for state-of-the-art food allergen risk assessment. This paper contributes to a harmonization of food allergen risk assessment and risk management and PAL practices.

1. Introduction

Allergen management is a crucial element of food safety management to protect allergic consumers from allergic reactions upon consumption of food intentionally or unintentionally containing allergenic proteins. In most regions of the world, existing regulations obligate food business operators to label the intentional use of priority allergens, as defined by particular jurisdictions. However, the use or absence of allergenic ingredient declarations is not always in agreement with actual presence or absence of allergenic ingredients in food products. Furthermore, no clear regulations exist for the communication regarding potential Unintended Allergen Presence (UAP) in food and the use of precautionary allergen labeling (PAL) statements. Food allergic consumers therefore cannot always rely on the information regarding allergen presence, or the absence of reference to certain allergens, on food labels, particularly regarding UAP. This poses significant risks to the food allergic consumer, as shown previously for instance by Spanjersberg et al. (2010), Remington et al. (2015) and Blom et al. (2018).

As in all areas of food safety management, elimination of all risks is impossible and it is key to strike the right balance between minimizing risks on the one hand and feasibility and practicality of management measures on the other hand, and at the same time to account for potentially competing societal priorities, such as minimizing food waste. For this, it is crucial to understand the risk associated with certain concentrations of allergenic protein in a food product. The overall risk is dependent upon both the concentration of the allergenic protein in the food product and the quantities of that food that may be eaten by allergic consumers. Together, these two factors determine the doses of allergenic protein that consumers are exposed to. These exposure doses, together with the sensitivity distribution of the allergic individuals, determines

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https://doi.org/10.1016/j.fct.2020.111831
Received 30 July 2020; Received in revised form 8 October 2020; Accepted 23 October 2020
Available online 7 November 2020

the probability of an allergic reaction, for instance expressed as the proportion of the at risk population that will react if the food containing the allergenic protein is used by this population. If the risk is to be considered in a broader public health dimension, other factors such as the number of product units available for consumption at any one time or in a certain time period may be factored in the risk calculation.

The last decade we saw a great advance in risk analysis of allergenic proteins in food by combining and analyzing information from different oral food challenge studies. Taylor et al. (2014) published results of analyses of thresholds for allergic reactions of about 1750 individual patients for 11 different allergenic foods. These analyses were based on data from low-dose food challenges in food allergic subjects that were systematically collected by the Netherlands Organisation for Applied Scientific Research (TNO) and the Food Allergy Research and Resources Program (FARRP) of the University of Nebraska-Lincoln, USA. Reference Doses (RDs) based on doses predicted to elicit mild objective allergic symptoms in no more than 1–5% of the allergic population were proposed. These RDs were intended to balance minimizing risks for allergic consumers and feasibility in implementing RDs for food business operators. The RDs can be used to calculate Action Levels (ALs) for Precautionary Allergen Labeling (PAL) of food products. These RDs were adopted by the Allergen Bureau of Australia & New Zealand in 2012 and implemented in their Voluntary Incidental Trace Allergen Labeling (VITAL) program (http://allergenbureau.net/vital/) as VITAL Version 2.0 RDs (Taylor et al., 2014; Allen et al., 2014). The VITAL RDs are increasingly being used by food business operators worldwide to guide their allergen risk management including the calculation of ALs for PAL. Also patient groups welcome the use of RDs as evidence-based approach to the application of precautionary allergen labelling (DunnGalvin 2019). In recent years, also several food safety authorities of north-western European countries have adopted the principle of using RDs as a benchmark in their allergen risk assessment and management (BVL 2015; Bolin and Lindeberg 2016; NVWA 2016; FASFC 2017; Waiblinger and Schulze 2018).

The RDs proposed by Taylor et al. (2014) are expressed in mg total protein from the allergenic food. Levels of allergenic substance in food complying with RDs and ALs for PAL can be derived from these RDs by selecting appropriate food intake figures and using the following equation:

$$\mathrm{AL(in\ mg\ total\ protein\ from\ the\ allergenic\ food/kg\ food)} = \frac{\mathrm{RD(in\ mg\ total\ protein\ from\ the\ allergenic\ food)}}{\mathrm{Amount\ of\ food\ consumed(in\ kg)}}$$

In this equation, the “Amount of food consumed” refers to the amount consumed on a single eating occasion of a food product in which a certain amount of protein from an allergenic food is present (also see Discussion section).

Since the 2014 publication of the RDs by Taylor et al. (2014), TNO and FARRP continued systematically collecting threshold data and increased the number of available and useful datapoints from about 1750 to over 3400 for 14 different allergenic foods. In collaboration with a large panel of experts, including many clinicians internationally, TNO and FARRP recently published a consensus paper specifying how outcomes from food challenges are used to derive individual patients’ No-Observed-Adverse-Effect-Levels (NOAELs) and Lowest-Observed-Adverse-Effect-Levels (LOAELs) for objective symptoms (Westerhout et al., 2019), which are needed to derive population threshold dose distributions for objective symptoms (Taylor et al., 2009). Population threshold dose distribution modelling uses different statistical models (Taylor et al., 2014), where the estimated RD is model-dependent. As there is frequently no biological or statistical basis for preferring one model over another, the use of different models results in different risk predictions (predicted proportions reacting) for the same dose of protein. Previously, the RDs from different models were derived by applying expert judgement, including judgement of the fit of the various models with the actual challenge data, with emphasis on the region encompassing the ED01 and ED05. To reduce the subjectivity and uncertainty of choosing a RD from a single statistical model it is possible to apply Bayesian model averaging (Hoeting et al., 1999) or Bayesian Stacking (Yao et al., 2018). These techniques, hereafter generically referred to as model averaging, are statistical approaches that derive a single outcome based on different models while accounting for the degree of fit of the various models with the actual datapoints (EFSA Scientific Committee 2017; US EPA et al., 2019). Until recently, software for model averaging methods was not available for analyzing the interval-censored dose-to-failure distributions obtained for allergic symptoms in oral food challenges. TNO and FARRP therefore entered into collaboration with international experts in model averaging and developed a model averaging method, based upon Bayesian Stacking (Yao et al., 2018), suitable for modeling dose-to-failure distributions for allergy thresholds (Wheeler et al., 2020). Using all these achievements, we recently updated our threshold dose distribution analyses for 14 allergenic foods and published doses (and their 95% confidence intervals) that are predicted to elicit mild objective allergic symptoms in 1% (the Eliciting Dose 01 or ED01) or 5% (ED05) of the allergic population (Remington et al., 2020). The ED01 values from this publication were adopted by the Allergen Bureau of Australia & New Zealand in a VITAL program update in 2019 and implemented as VITAL Version 3.0 RDs (http://allergenbureau.net/vital/).

In the publication by Remington et al. (2020), the ED01 and ED05 values were specifically presented and discussed in the framework of establishing RDs for allergen management and the calculation of ALs for PAL. Besides for the elaboration of RDs, population threshold dose distributions can also be used to characterize the risks of other, broader ranges of doses of allergenic proteins. This would be of value for the quantification of risks when a certain concentration of (unintended) allergenic protein is found in a food product. Risk assessors and risk managers therefore would benefit from accessibility to a broader range of ED values for the various allergenic foods. The recently developed model averaging method enables the publication of unique single ED values. In this paper, we provide these ED values for the 14 priority allergenic foods and give recommendations for their use, specifically in the context of characterizing the risks of various concentrations of (unintended) allergenic proteins in food products, in this paper generally expressed as the predicted proportion of reactions in the at-risk population.

2. Data and methods

Full details on the methods for deriving the population threshold dose distributions for 14 priority allergenic foods and the data used are given in Remington et al. (2020). In brief: individual patients’ NOAELs and LOAELs for the elicitation of objective allergic symptoms were established from publications and unpublished clinical records of low-dose oral challenges using criteria as published previously by

Westerhout et al. (2019). Only data from double-blind, placebo-controlled food challenges (DBPCFCs) were used, except in case of data from infants and very young children and for wheat. The data were collected and assessed in terms of discrete dose and cumulative dose datasets and expressed in mg of total protein from the allergenic food. Individuals were left-censored if they reacted with objective symptoms to the first challenge dose, while individuals were right-censored if they failed to respond with objective symptoms to the uppermost challenge dose but did have clear histories of allergic reactions upon consumption of the offending food.

Individual studies were combined per allergenic food and analyzed with the Model Averaging approach developed by Wheeler et al. (2020). The approach combines five parametric survival distributions (Weibull distribution, Log-Gaussian (or Log-Normal), Log-Logistic, Generalized Pareto and Log-Laplace (or Log-Double-Exponential)) into a single model averaging outcome that was used to determine population EDs on the basis of both discrete dosing and cumulative dosing. The method is based upon a Bayesian stacking methodology and estimates dose-to-failure based upon Markov chain Monte Carlo (MCMC) simulation. As this methodology is a stochastic approximation based upon simulation, final ED estimates can have small variations. Because the method requires large amounts of computer resources, a single MCMC chain cannot be run to the required length to minimize Monte Carlo error. Instead, to minimize variability, the stacked model averaging estimation procedure is repeated independently 10 times and the mean of 10 ED estimates is used as a central estimate. For each allergenic food, the random sampling procedure is truncated at the highest given dose (discrete or cumulative), based on all of the studies included in the dataset for that specific allergenic food, as extrapolation beyond the highest given dose would lead to a change in the model average survival curve, resulting in overestimation of lower ED values (also see Discussion section).

3. Results

3.1. Eliciting Dose values from model averaged population threshold dose distributions for 14 priority allergenic foods

Table 1 gives ED01 to ED10 and ED15, ED20, ED25, and ED50 values from the model averaged population threshold dose distributions for the 14 priority allergenic foods. Both the EDs based on the discrete and the cumulative dose datasets are given. Full lists of ED values based on discrete (Table S1) and cumulative (Table S2) dose datasets with incremental steps of 0.1 from the ED0.1 to the ED0.9 and steps of 1 from the ED01 to the ED99 are given as supplementary data.

3.2. Eliciting Dose curves from model averaged population threshold dose distributions for 14 priority allergenic foods

Fig. 1 gives the curves of the ED values from the model averaged population threshold dose distributions for the 14 priority allergenic foods, based on the discrete and cumulative dose datasets.

4. Discussion and recommendations for use of ED values in risk characterization

The ED01 and ED05 values for the 14 allergenic foods published by us previously (Remington et al., 2020) were presented and discussed specifically in the context of establishing RDs for allergen management and the calculation of ALs for PAL. The publication of the broad range of ED values for these allergenic foods in the current paper is meant to support the characterization of the risk associated with the (unintended) presence of allergenic proteins in food products by providing the doses of allergenic protein to which defined proportions of the at-risk population are predicted to react. Allergen risk characterization can be applied to inform risk managers for example in cases of unintended presence of allergens or mislabeling (absence) of allergenic ingredients in food products on the market or to assess the efficacy of cleaning procedures. However, population ED values are only one of the elements needed for the characterization of risks of allergens in food. The ED values need to be accessed in combination with information on concentrations of allergenic proteins in food products and information on food intake. A risk assessment further needs to be attuned to the risk management question which should specify the outcomes of interest and the outcomes should be expressed and interpreted in a correct way. For instance, is the risk assessment outcome to be expressed as the proportion of allergic individuals that will react if a food containing an allergenic protein is used by them, or as the number of people expected to react considering the number of product units available in a certain region or period of time? Several choices need to be made that determine the correctness of the outcomes and the suitability for the purpose of the risk assessment. Therefore, in this section, we provide some recommendations for the use of the presented ED values to support risk assessors and risk managers in the application and interpretation of these for the characterization of risks of concentrations of (unintended) allergenic proteins in food products. In addition, we discuss several aspects of the datasets and ED values that are relevant for the applicability and suitability in use.

4.1. "Larger than" values and cut-off curves

In Table 1 and Tables S1 and S2 sometimes "larger than" (>xx) values are reported, and in Fig. 1 some curves do not run up to the 100% cumulative percentage of responders. This is due to truncated random sampling procedures. As indicated in section 2. Data and methods, for each allergen, the random sampling procedure is truncated at the highest dose (discrete or cumulative) given in the clinical challenges in the studies included in the dataset for that specific allergen. Extrapolation beyond this dose would possibly lead to a slight change in the model average survival curve, resulting in overestimation of the lower ED values and thus an underestimation of risks of low doses of allergenic protein. To avoid this, the random sampling procedures were truncated as described. Due to the truncation, it is not possible to estimate the high ED values for some of the allergens as these values would be higher than the highest given dose in challenge studies. Therefore, "larger than" (>xx) values are reported in the tables in these cases and some of the curves in Fig. 1 are cut off at some point. Yet, ED values up to at least the ED70 are available for all 14 allergenic foods.

4.2. Discrete versus cumulative dose datasets

As already discussed by Remington et al. (2020), in the challenge trials from which the ED values were derived, increasing doses were given with short intervals (usually between 15 and 30 min) to identify the patient's NOAEL and LOAEL. It cannot be excluded that in some cases a previous dose may have contributed to the total dose triggering allergic symptoms and using cumulative doses for establishing the NOAELs and LOAELs might be appropriate. However, allergic symptoms may well develop within minutes after allergen intakes, indicating that discrete doses may also be appropriate to use. This paper therefore, similarly as done by Remington et al. (2020), presents results from both discrete and cumulative dose datasets.

The ED values derived from the discrete dose datasets are often slightly lower than those derived from the cumulative dose datasets. However, there are cases where the ED values derived from the cumulative datasets, particularly low ED values, are slightly lower than the values derived from the discrete datasets (see for instance the low ED values for mustard, celery or fish in Table 1 and Supplementary Tables S1 and S2). Although the differences are rather small, it is recommended to consider both the discrete and cumulative dose datasets in all risk assessments and use the ED value or percentage of predicted responders that is most appropriate for the purpose of the assessment at

Table 1
ED01 to ED10 and ED15, ED20, ED25, and ED50 values from the model averaged population threshold dose distributions for 14 priority allergenic foods, based on discrete (A) and cumulative (B) dose datasets. The 95% confidence interval is represented by the lower confidence interval (LCI) and the upper confidence interval (UCI). ED values are expressed in mg total protein from the allergenic food.

A. Discrete dose datasets

ED	Cashew	LCI	UCI	Celery	LCI	UCI	Egg	LCI	UCI	Fish	LCI	UCI
ED01.0	0.05	0.02	0.3	0.07	0.02	1.9	0.2	0.1	0.5	2.6	1.0	12.0
ED02.0	0.1	0.04	0.9	0.3	0.04	4.0	0.6	0.3	1.3	4.8	1.8	20.1
ED03.0	0.3	0.08	1.9	0.6	0.1	6.4	1.1	0.5	2.3	7.1	2.7	28.0
ED04.0	0.5	0.1	3.3	1.0	0.2	9.0	1.6	0.8	3.4	9.5	3.6	35.8
ED05.0	0.8	0.2	5.0	1.5	0.3	11.8	2.3	1.2	4.7	12.1	4.5	43.9
ED06.0	1.2	0.3	7.1	2.2	0.5	15.0	2.9	1.6	6.1	14.7	5.6	52.2
ED07.0	1.6	0.4	9.5	2.9	0.6	18.3	3.7	2.0	7.5	17.5	6.6	60.8
ED08.0	2.1	0.6	12.3	3.8	0.8	22.0	4.5	2.4	9.1	20.4	7.8	69.8
ED09.0	2.7	0.7	15.5	4.8	1.1	25.9	5.4	2.9	10.8	23.5	9.0	79.0
ED10.0	3.4	0.9	19.0	5.9	1.4	30.2	6.3	3.4	12.6	26.7	10.2	88.7
ED15.0	7.8	2.1	42.7	13.0	3.3	55.8	11.8	6.5	22.9	45.5	17.6	143
ED20.0	14.5	3.9	77.5	23.3	6.2	89.9	18.5	10.4	35.5	69.2	27.0	210
ED25.0	23.9	6.3	125	36.9	10.3	134	26.7	15.0	50.5	99.1	38.8	293
ED50.0	139	34.7	666	180	55.2	596	94.5	53.1	173	418	163	1146
ED	**Hazelnut**	**LCI**	**UCI**	**Lupin**	**LCI**	**UCI**	**Milk**	**LCI**	**UCI**	**Mustard**	**LCI**	**UCI**
ED01.0	0.1	0.07	0.6	2.9	1.3	9.1	0.2	0.1	0.5	0.07	0.009	1.1
ED02.0	0.6	0.2	2.1	5.9	2.6	18.4	0.6	0.3	1.3	0.1	0.03	1.8
ED03.0	1.3	0.4	4.5	8.9	4.0	27.8	1.1	0.5	2.4	0.2	0.05	2.4
ED04.0	2.3	0.8	7.8	12.1	5.3	37.3	1.7	0.9	3.6	0.3	0.07	3.0
ED05.0	3.5	1.3	12.1	15.3	6.7	47.0	2.4	1.3	5.0	0.4	0.1	3.6
ED06.0	5.1	1.8	17.2	18.6	8.1	56.9	3.2	1.7	6.6	0.6	0.1	4.3
ED07.0	6.9	2.5	23.2	21.9	9.6	66.9	4.1	2.1	8.3	0.7	0.2	5.0
ED08.0	9.0	3.3	30.1	25.4	11.1	77.1	5.0	2.7	10.1	0.8	0.2	5.7
ED09.0	11.4	4.3	38.0	28.9	12.6	87.5	6.0	3.2	12.1	0.9	0.2	6.5
ED10.0	14.1	5.3	46.8	32.5	14.1	98.1	7.1	3.8	14.2	1.1	0.3	7.3
ED15.0	32.4	12.4	105	51.9	22.2	154	13.8	7.5	26.7	1.9	0.4	11.9
ED20.0	59.2	22.8	190	73.8	31.1	215	22.2	12.3	42.5	2.9	0.7	17.5
ED25.0	95.5	37.0	302	98.4	41.0	283	32.7	18.2	61.8	4.2	1.0	24.3
ED50.0	489	183	1405	287	113	781	125	70.1	227	17.2	3.6	88.4
ED	**Peanut**	**LCI**	**UCI**	**Sesame**	**LCI**	**UCI**	**Shrimp**	**LCI**	**UCI**	**Soy**	**LCI**	**UCI**
ED01.0	0.2	0.1	0.4	0.1	0.03	2.7	26.2	2.7	166	0.5	0.2	3.5
ED02.0	0.4	0.2	1.2	0.4	0.07	7.8	75.6	10.9	336	1.5	0.4	11.2
ED03.0	0.9	0.5	2.1	1.0	0.1	14.8	137	24.8	512	3.5	0.7	22.4
ED04.0	1.5	0.8	3.3	1.7	0.2	23.4	205	44.3	693	6.3	1.2	36.9
ED05.0	2.1	1.2	4.6	2.7	0.4	33.6	280	69.3	880	10.0	2.2	54.6
ED06.0	2.9	1.7	6.0	3.8	0.6	45.3	360	99.5	1072	14.5	3.3	75.6
ED07.0	3.8	2.2	7.7	5.1	0.8	58.4	445	135	1271	19.9	4.6	99.8
ED08.0	4.8	2.8	9.4	6.7	1.1	72.9	534	175	1475	26.3	6.3	127
ED09.0	5.9	3.4	11.3	8.4	1.5	88.9	627	219	1687	33.6	8.3	158
ED10.0	7.1	4.1	13.4	10.3	1.9	106	723	268	1903	41.9	10.6	192
ED15.0	14.6	8.6	26.3	22.8	4.7	214	1258	560	3089	99.1	27.1	419
ED20.0	24.7	14.8	43.6	40.2	9.0	355	1876	907	4457	186	53.4	748
ED25.0	37.7	22.7	65.7	62.9	14.7	530	2583	1289	6031	308	91.1	1197
ED50.0	165	99.0	282	306	66.1	1988	7906	3757	17917	1779	547	6459

ED	Walnut	LCI	UCI	Wheat	LCI	UCI
ED01.0	0.03	0.01	0.5	0.7	0.3	2.5
ED02.0	0.1	0.02	1.6	1.8	0.7	5.4
ED03.0	0.3	0.04	3.4	3.1	1.3	8.6
ED04.0	0.5	0.06	5.8	4.6	1.9	12.0
ED05.0	0.8	0.1	8.9	6.1	2.6	15.6
ED06.0	1.2	0.2	12.7	7.8	3.4	19.4
ED07.0	1.7	0.2	17.2	9.6	4.2	23.3
ED08.0	2.3	0.3	22.4	11.4	5.1	27.4
ED09.0	3.0	0.4	28.3	13.4	6.1	31.6
ED10.0	3.8	0.6	35.0	15.4	7.1	35.9
ED15.0	9.7	1.5	81.1	26.9	12.8	59.6
ED20.0	19.3	3.1	152	40.3	19.7	86.9
ED25.0	33.5	5.5	252	55.9	27.6	118
ED50.0	235	37.8	>1050	174	87.7	344

B. Cumulative dose datasets

ED	Cashew	LCI	UCI	Celery	LCI	UCI	Egg	LCI	UCI	Fish	LCI	UCI
ED01.0	0.09	0.04	0.5	0.05	0.02	0.5	0.2	0.1	0.5	1.3	0.4	12.7
ED02.0	0.3	0.09	1.8	0.2	0.04	1.6	0.6	0.3	1.4	3.9	1.0	29.0
ED03.0	0.6	0.2	3.7	0.4	0.07	3.2	1.1	0.5	2.5	7.2	1.8	49.7
ED04.0	1.0	0.3	6.2	0.8	0.1	5.3	1.7	0.9	3.8	11.1	3.1	74.3
ED05.0	1.6	0.4	9.4	1.3	0.2	7.9	2.4	1.3	5.3	15.6	4.6	102

(*continued on next page*)

Table 1 (*continued*)

B. Cumulative dose datasets

ED	Cashew	LCI	UCI	Celery	LCI	UCI	Egg	LCI	UCI	Fish	LCI	UCI
ED06.0	2.3	0.6	13.2	1.8	0.4	11.0	3.3	1.7	6.9	20.6	6.4	134
ED07.0	3.1	0.8	17.6	2.5	0.5	14.6	4.2	2.2	8.7	26.2	8.3	169
ED08.0	4.0	1.1	22.6	3.4	0.7	18.7	5.2	2.7	10.7	32.2	10.5	206
ED09.0	5.0	1.3	28.2	4.3	0.9	23.2	6.2	3.3	12.8	38.7	12.8	247
ED10.0	6.2	1.7	34.6	5.4	1.2	28.3	7.4	3.9	15.1	45.6	15.3	290
ED15.0	14.0	3.8	76.2	13.0	3.1	61.7	14.4	7.8	28.5	87.6	30.1	545
ED20.0	25.6	7.0	136	24.6	6.1	110	23.4	12.8	45.6	142	48.7	858
ED25.0	41.7	11.3	217	41.1	10.5	177	34.6	19.1	66.6	208	71.5	1225
ED50.0	232	59.5	1106	246	66.5	957	134	74.5	250	793	267	3822
ED	**Hazelnut**	**LCI**	**UCI**	**Lupin**	**LCI**	**UCI**	**Milk**	**LCI**	**UCI**	**Mustard**	**LCI**	**UCI**
ED01.0	0.2	0.09	0.7	2.6	0.5	14.8	0.3	0.2	0.6	0.05	0.006	0.9
ED02.0	0.7	0.2	2.7	5.8	1.4	28.5	0.7	0.4	1.6	0.1	0.02	1.6
ED03.0	1.7	0.6	5.8	9.3	2.4	42.2	1.3	0.7	3.0	0.2	0.04	2.3
ED04.0	3.0	1.1	10.1	13.0	3.5	55.9	2.1	1.1	4.6	0.3	0.06	3.1
ED05.0	4.7	1.7	15.7	16.8	4.7	70.0	3.1	1.6	6.6	0.5	0.09	3.9
ED06.0	6.8	2.5	22.5	20.8	6.0	84.1	4.1	2.1	8.7	0.6	0.1	4.8
ED07.0	9.3	3.4	30.5	25.0	7.4	98.6	5.3	2.8	11.1	0.8	0.2	5.8
ED08.0	12.2	4.5	39.8	29.3	8.9	113	6.6	3.5	13.7	0.9	0.2	6.9
ED09.0	15.5	5.8	50.4	33.7	10.4	128	8.1	4.2	16.6	1.1	0.2	8.0
ED10.0	19.3	7.3	62.4	38.3	12.0	144	9.6	5.1	19.6	1.3	0.3	9.2
ED15.0	44.9	17.2	143	63.3	21.0	225	19.1	10.3	38.1	2.5	0.6	16.4
ED20.0	83.1	32.1	260	92.3	31.7	316	31.6	17.2	62.0	4.1	0.9	25.8
ED25.0	136	52.7	419	126	44.2	419	47.3	25.8	91.7	6.2	1.4	37.6
ED50.0	728	276	2064	402	144	1254	192	106	359	29.4	5.9	154
ED	**Peanut**	**LCI**	**UCI**	**Sesame**	**LCI**	**UCI**	**Shrimp**	**LCI**	**UCI**	**Soy**	**LCI**	**UCI**
ED01.0	0.7	0.5	1.3	0.2	0.04	4.8	30.8	3.4	326	0.7	0.3	4.5
ED02.0	1.5	1.1	2.6	0.7	0.09	13.8	98.3	14.3	676	2.0	0.6	15.0
ED03.0	2.3	1.6	4.0	1.5	0.2	25.8	190	33.1	1047	4.8	1.0	30.5
ED04.0	3.1	2.2	5.5	2.7	0.3	40.5	301	59.8	1440	8.8	1.7	51.0
ED05.0	3.9	2.8	7.1	4.2	0.6	57.7	429	94.0	1854	14.1	3.1	76.2
ED06.0	4.8	3.4	8.8	6.0	0.9	77.3	571	136	2293	20.8	4.7	106
ED07.0	5.8	4.1	10.6	8.1	1.3	99.1	727	185	2753	28.8	6.7	141
ED08.0	6.8	4.8	12.6	10.4	1.7	123	895	242	3237	38.2	9.2	181
ED09.0	7.9	5.5	14.8	13.1	2.3	149	1074	305	3745	49.2	12.2	226
ED10.0	9.0	6.2	17.3	16.1	2.9	178	1265	376	4274	61.6	15.6	277
ED15.0	16.8	10.6	34.0	35.1	7.3	350	2377	823	7299	149	41.2	613
ED20.0	30.8	17.0	56.8	61.1	13.7	574	3745	1415	11007	284	82.5	1110
ED25.0	48.2	28.2	87.1	94.3	22.1	847	5374	2132	15457	475	143	1801
ED50.0	236	138	412	443	91.5	2993	18867	7690	52732	2858	903	10140

ED	Walnut	LCI	UCI	Wheat	LCI	UCI
ED01.0	0.04	0.02	0.6	1.1	0.4	3.8
ED02.0	0.1	0.03	2.3	2.8	1.0	8.5
ED03.0	0.4	0.06	4.9	4.7	1.9	13.6
ED04.0	0.7	0.09	8.4	6.9	2.8	19.1
ED05.0	1.2	0.1	13.0	9.3	3.9	24.9
ED06.0	1.7	0.2	18.6	11.9	5.0	31.0
ED07.0	2.5	0.3	25.2	14.7	6.3	37.4
ED08.0	3.3	0.5	33.0	17.6	7.7	44.0
ED09.0	4.4	0.6	41.9	20.7	9.1	50.9
ED10.0	5.6	0.8	52.0	23.9	10.6	58.1
ED15.0	14.3	2.2	122	41.9	19.3	97.4
ED20.0	28.7	4.6	231	63.3	29.7	143
ED25.0	50.2	8.2	386	88.1	41.9	194
ED50.0	360	57.0	>1693	279	135	578

hand. This will generally be the one that, from a precautionary principle, gives the most conservative risk characterization (i.e. the risk of a certain concentration of allergenic protein in food is assumed a bit higher).

4.3. Establishment of the percentage of responders to be expected for a dose of allergenic substance

The percentage of allergic individuals expected to experience objective allergic symptoms when consuming a certain dose of protein from an allergenic food can be retrieved by using the ED value tables presented in this paper. For example, for a dose 0.8 mg total cashew protein, the discrete dose dataset predicts that around 5% (2–9% based on the confidence intervals) of the cashew allergic individuals will show an objective allergic reaction (see Table 1 and Supplementary data Table S1). The cumulative dose dataset predicts that between 3 and 4% (2–7% based on the confidence intervals) of the cashew allergic individuals will have an objective allergic reaction (Table 1 and Supplementary data Table S2). Appropriate use of the ED value tables and correct determination of the percentage responders to be expected for a certain dose of allergenic substance depend on a correct establishment and expression of the dose to use for comparison with the ED values, which is addressed in the following paragraph.

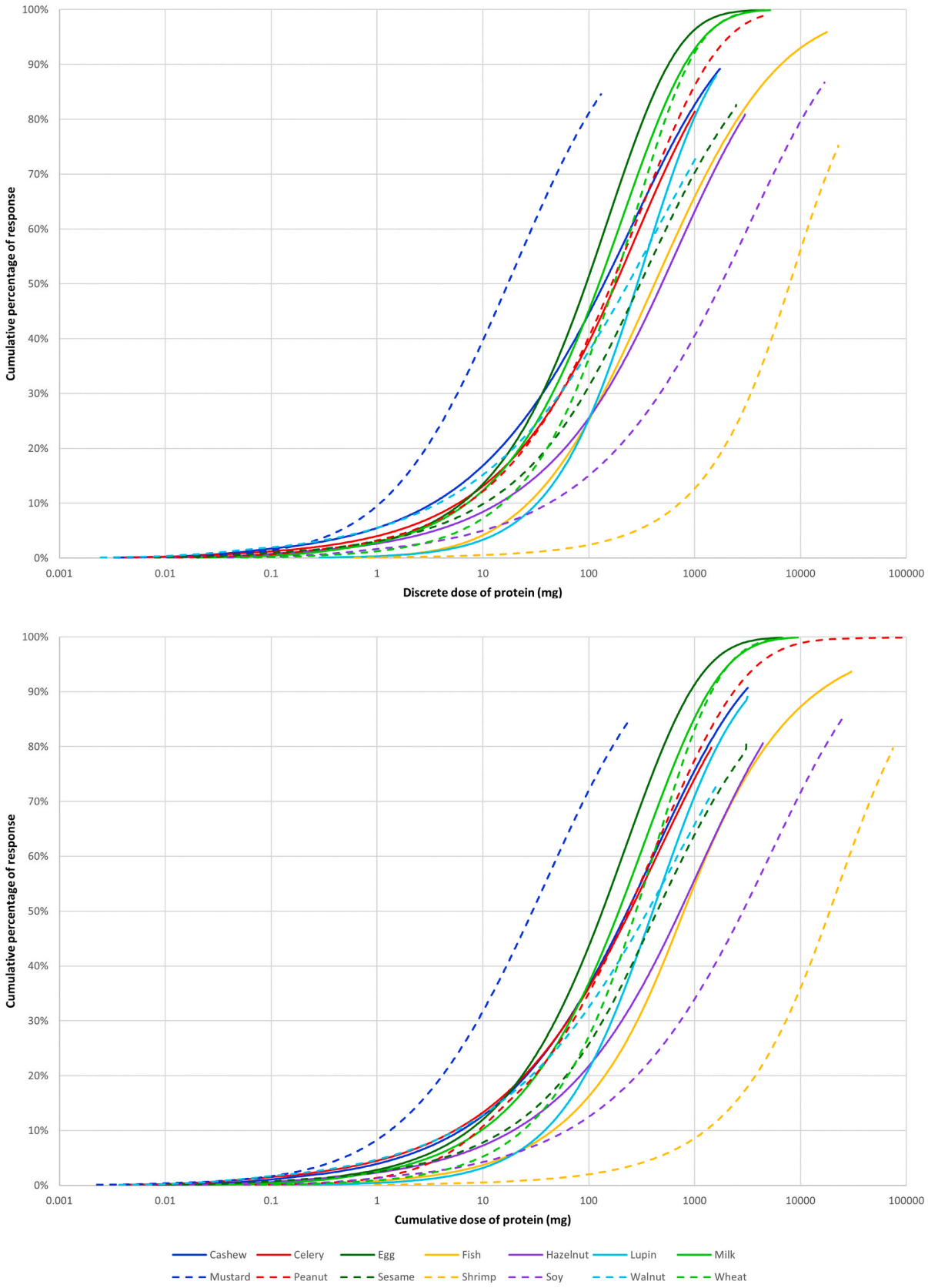

Fig. 1. ED curves from the model averaged population threshold dose distributions for 14 priority allergenic foods, based on discrete (upper graphs) and cumulative (lower graphs) dose datasets. Doses are expressed in mg total protein from the allergenic food.

4.4. Establishment and expression of the dose of allergenic substance

The ED values given in this paper are doses expressed in mg total protein from the allergenic food. For the quantification of the risk associated with a certain concentration of allergenic substance in a food, this concentration needs to be transformed into a dose of allergenic substance by multiplying it by the amount of the food consumed at a single eating occasion using the following equation and reporting units:

$$\frac{\text{Concentration of allergenic substance}}{\text{(in mg total protein from the allergenic food/kg food)}} \times \text{Amount of food consumed(in kg)} = \frac{\text{Dose of allergenic substance}}{\text{(in mg total protein from the allergenic food)}}$$

Again, "Amount of food consumed" refers to the amount consumed of a food product in which a certain amount of protein from an allergenic food is present.

4.4.1. Amount of food consumed

Food allergic reactions generally develop rapidly (within half an hour) and the amount of allergenic protein consumed within a short period of time determines the relevant dose for use in the risk assessment of allergenic protein in food. Therefore, the amount of a food consumed at a single eating occasion is to be used for establishing the dose, rather than for instance daily intakes (Spanjersberg et al., 2007; Kruizinga et al., 2008). Preferably, data derived from surveys on real food intake should be used. Recommended serving sizes provided by, for instance, food manufacturers or nutritional guides, refer to single eating occasions but should NOT be used, because they generally are provided for nutritional purposes, e.g. to discourage the use of large amounts of high caloric foods, and generally do not reflect real intakes. However, also from data on real food intake, various intake figures can be selected for single eating occasions, ranging from the mean, various percentile (P)-values (e.g. P75, P80, P90., P95, P97.5) or even maximum values. It should be realized that using higher intake values results in more conservative risk assessments that may overestimate the actual risks. Although this appears safe from a risk management perspective, using too high intake figures may miss the right balance between being protective on one hand and being practical and feasible to implement on the other hand and thus may not optimally inform risk managers. It therefore is crucial to carefully consider the selection of the most appropriate food intake figure when performing a risk assessment.

The importance of selecting an appropriate intake figure was clearly illustrated by Blom et al. (2019), who performed sensitivity analyses to establish what food intake point estimate is most appropriate for use in deterministic food allergen risk assessment in the context of applying RDs as proposed by Taylor et al. (2014). They showed that using the P50 intake of a food product in the population of users of the product provides a deterministic risk assessment outcome as safe as a probabilistic risk assessment for 99% of the food groups. Using the P75 resulted in a deterministic risk assessment outcome as safe as the one calculated through probabilistic modelling for all food groups. In these analyses, a probabilistic risk assessment was used as a reference, as this approach is generally considered the most appropriate method for population risk assessment and management purposes (Madsen et al., 2009). Based on these results, the P75 was recommended for use as a point estimate in deterministic risk assessment for compliance with RDs as proposed by Taylor et al. (2014) rather than higher intake figures. The P75 is sufficiently conservative and provides a good balance between compliance with the predefined food safety objective and feasibility and practicality of management measures (Blom et al., 2019). A list of population p75 intakes at single eating occasions for a broad range of food groups was developed by combining food consumption data from various north-western European countries and was published by Birot et al. (2018).

4.4.2. Reporting units

Concentrations, amounts and doses of allergenic substances can be expressed in various reporting units (e.g. based on whole peanut, peanut butter or defatted peanut flour, raw whole egg, dried whole egg or dried egg white, crushed sesame seeds or sesame seed flour, milk or milk protein). Whole allergenic food amounts, processed allergenic food or fraction amounts and amounts of total protein from these foods can be converted into each other (Taylor et al., 2014). As the ED values given in this paper are doses expressed in mg total protein from the allergenic food, results from analyses always need to be carefully checked regarding reporting units used and, if required, converted into mg total protein from the allergenic food to allow comparison with the ED values given in this paper. For example, if from analyses it is reported that a food product contains 30 mg of milk/100 g food product, this equals about 1 mg of milk protein/100 g if liquid milk is used as reporting unit, based on a protein content of milk of 3.3% (Taylor et al., 2014). If this food product would concern a herb or spices mix, bouillon cube, or yeast extract, the north-western European population p75 intake at a single eating occasion would be about 20 g (Birot et al., 2018). An intake of 20 g of such food product would lead to a dose of about 0.2 mg of protein from milk, which is the right unit to compare with the ED values presented in this paper. Supplementary Tables S1 and S2 show that this dose will be unlikely to elicit objective allergic symptoms in more than 1% of the milk allergic population. This dose does not exceed the VITAL 3.0 RD for milk of 0.2 mg protein from milk (http://allergenbureau.net/vital/) and indicates that allergic reactions that incidentally might be triggered generally will be mild (Remington et al., 2020). However, if it is reported that such food product contains 30 mg of milk protein/100 g food product, the dose resulting from intake of 20 g of such food product would be 6 mg of protein from milk. This dose equals the discrete dose dataset ED09 (Supplementary Table S1), indicating that 9% of the milk allergic patients may be expected to suffer objective allergic symptoms. The predicted risk from the cumulative dose dataset is in the same range but slightly lower than the risk predicted by the discrete dose dataset (the dose of 6 mg is between the cumulative dose dataset ED07 and ED08 (Supplementary Table S2), suggesting between 7 and 8% of responders with objective symptoms). From a precautionary approach, the 9% responders predicted by the discrete dose dataset should be used. The potential for some milk-allergic consumers to experience severe reactions at such doses is unknown but cannot be easily excluded.

4.5. Deterministic versus probabilistic risk assessment

As indicated above, probabilistic risk assessment is considered the most appropriate method for population allergen risk assessment and management purposes (Madsen et al., 2009; Crevel et al., 2014). The ED values presented in this paper can be used for probabilistic risk assessment. However, for such advanced risk assessment, specific expertise, advanced statistical modelling programs and experience and additional datasets like population single eating occasion food intake distributions are needed (Spanjersberg et al., 2010; Rimbaud et al., 2010; Remington et al., 2015; Blom et al. 2017, 2018). These conditions cannot always be met by all risk assessors and the ED values can then be used for deterministic risk assessment as an alternative, if the recommendations given

in the previous paragraphs are followed. Such a deterministic approach may be opportune for many risk management goals or can be performed as a first-tier risk assessment. In case where an appropriate deterministic risk assessment does not indicate a risk in excess of what is considered tolerable, a more advanced risk assessment may not be needed. If a risk in excess of what is considered tolerable cannot be excluded based on a deterministic risk assessment, risk mitigation measures can be applied whenever possible, or a more advanced probabilistic risk assessment involving experienced experts with access to the required models and datasets can be considered to more precisely characterize the risks.

4.6. Reliability, representativeness and robustness of ED values and uncertainties in risk assessment

Considerable research has been done to investigate the reliability, representativeness and robustness of ED values as elaborated. A major achievement was published by Hourihane et al. (2017), who, using a novel single dose challenge protocol, documented that dosing peanut allergic individuals at the ED05 only resulted in mild symptoms. Further, their observation that at the ED05 only 2.3% of the challenged individuals showed predefined positive reactions, indicates that either some selection bias occurred or that the approach used to elaborate the ED values introduces some conservatism, providing a small undocumented additional safety margin. For a summary and discussion of this and other studies on the safety of ED values we refer to the discussion section of our previous paper in which we published the ED01 and ED05 values in the context of establishing RDs (Remington et al., 2020). Most datasets contained over 60 datapoints, while Klein Entink et al. (2014) reported that above 60 datapoints, ED estimates are relatively stable. Particularly for the datasets with low numbers of subjects, the data were carefully checked on irregular distributions, which would disqualify the data for modeling the ED distribution for the specific allergenic food. All data used were further carefully checked on methodological criteria, as specified in Remington et al. (2020), and the consensus methodology for elaborating NOAELs and LOAELs from the datasets as published by Westerhout et al. (2019) was applied. Finally, the model averaging method applied includes and combines different statistical models, uses predictive inference assigned weights to the various models based upon predictive accuracy, and best accounts for study-to-study heterogeneity (Wheeler et al., 2020) and avoids ED estimate differences by different statistical models, some of which sometimes poorly match the actual challenge data, as discussed by Taylor et al. (2014). As reported by Remington et al. (2020), "prior attempts to study possible differences between age groups or differences arising from variations in geographic location or challenge material have found no difference between the studies, or have been confounded by patient selection bias and differing study protocols/dosing schemes and no true differences could be observed". Therefore, all available data could be combined to derive the ED value distributions, suitable for direct use in risk assessment for each age group without the need to apply uncertainty corrections to these. However, other sources of uncertainly may exist when doing a risk assessment, for instance regarding representativeness of samples analyzed for allergenic substance concentrations or uncertainties regarding the amounts of food actually consumed by individuals at single eating occasions. These uncertainties may indicate the need for uncertainty corrections in a risk assessment, to be considered on a case-by-case basis for each risk assessment conducted. These uncertainties however are not unique to food allergen risk assessment as these apply generically to any domain of food risk assessment.

Although we thus acknowledge that there will be uncertainties, it should also be recognized that there is a rather unique advantage supporting the reliability of food allergen risk assessment based on ED values as we present in this paper. Scientific information has accumulated over the past decades and the reliability of data on the sensitivity of food allergic individuals enables a more reliable hazard characterization compared to many other areas of risk assessment and food safety standard setting. Numerous risk assessments have been conducted and standards have been set in toxicology, based on animal test data subject to significant uncertainties in the extrapolation to humans. The data published in this paper give insight into the sensitivity distribution specifically of the defined human subpopulation at risk of a food allergic reaction for which the risk assessment and risk management is performed. Remaining uncertainties in food allergen hazard, risk and safety assessment, based on this insight, will likely be negligible in comparison to uncertainties associated with many of the animal to human extrapolations as generally applied in toxicology.

4.7. Comparison of allergenic potencies of protein from different foods

The ED values presented in this paper allow comparison of the allergenic potencies of protein from different allergenic foods. The results show that allergenic potencies differ between foods. This particularly is clear from the ED distribution graphs given in Fig. 1. From this figure and Tables 1, S1 and S2, it is directly clear that mustard is the most potent allergenic food and soy and shrimp are least potent. For other allergenic foods, it sometimes is difficult to decide which allergenic food is more potent than another, as curves may cross each other. Previously, an Expert Group of the European branch of the International Life Science Institute (ILSI Europe) discussed the best value for comparing allergenic potencies of protein from different foods and concluded that the ED50 is the most suitable and robust parameter for this (Houben et al., 2016). This analysis was performed in the context of prioritization of allergenic foods for inclusion in allergen labeling legislation. The Expert group proposed and gave a proof of principle of using this parameter in combination with the prevalence of allergy for the allergenic foods in a 2-parameter scaling approach to express and compare the allergenicity of existing allergenic foods. A working group of the EU Cost Action project ImpARAS (https://imparas.eu) continued on this idea of a 2-parameter scaling approach to express and compare the allergenicity of foods. They presented a concept of using this scaling approach to develop a benchmark for the interpretation of results of allergenicity assessments of novel or modified food proteins (Houben et al., 2019). They also including a proof of principle applying this to allergenicity assessment results of insect proteins. The ED values published here may support efforts for developing criteria and methods also for the allergenicity risk assessment of novel (sustainable) food protein supply systems.

5. Final remarks

Our publication of the full range of ED values for the 14 EU priority allergenic foods is meant to support the characterization of risks posed by levels of (unintended) allergenic protein in food products. The information published in this paper can also be used to support the process of establishing and harmonizing RDs for risk management purposes, like for the calculation of ALs for PAL. It can be used in conjunction with industry guidance such as provided by the Allergen Bureau of Australia & New Zealand (Food Industry Guide to the Voluntary Incidental Trace Allergen Labelling (VITAL®) Program: http://allergenbureau.net/vital/) or FoodDrinkEurope (Guidance on Food Allergen Management for Food Manufacturers: https://www.fooddrinkeurope.eu/) to support food businesses at different levels in the supply chain. Currently, the use of PAL is not guided by harmonized regulation and differences in practices exist between companies or sectors as well as authorities from

different countries. The current situation poses significant risks to allergic consumers, as for instance shown by a recent prospective study on the occurrence of unexpected allergic reactions (Michelsen-Huisman et al., 2018; Blom et al., 2018) and there is an urgent need to improve and harmonize risk management and communication practices. It is not in the benefit of any of the stakeholders, and at least in the benefit of allergic consumers, if individual companies or individual authorities make their own and different choices in establishing RDs, and harmonization will benefit all stakeholders and most of all the allergic consumer. The establishment of a food safety objective and selection of ED values for establishing harmonized RDs for food allergen risk management and PAL by food business operators and regulatory agencies preferably should be supported through a process involving all stakeholders. An Expert Group of ILSI Europe recently analyzed and discussed various aspects of processes for establishing safety standards and proposed a framework for establishing a level of tolerable risk for allergen management based on criteria suggested by Murphy and Gardoni (2008) (Madsen et al., 2020). Based on these criteria, the Expert Group concluded that sufficient knowledge is available to apply the framework and move forward with developing a harmonized RD-based guidance for allergen risk management and the application of PAL.

One of the criteria derived from Murphy and Gardoni that Madsen et al. (2020) considered crucial for the establishment of a broadly accepted tolerable level of risk and RDs for PAL is that required data inputs are accurate, available and accessible. They indicated that a significant step towards common standards has been achieved with the recent publication of Westerhout et al. (2019) and that publication of full population ED-distribution details would provide important true availability and accessibility of input data. The data provided in this publication give risk assessors and risk managers this access to full population ED distribution information for 14 priority allergenic foods, based on the worldwide largest threshold database, using broad international consensus regarding suitable datapoints and methods to apply for establishing individual patient's NOAELs and LOAELs and state of the art statistical modelling, and enable them to use this in food allergen risk assessment and management. This paper therefore gives a strong contribution to a harmonization of food allergen risk assessment and risk management and PAL practices.

CRediT authorship contribution statement

Geert F. Houben: Conceptualization, Methodology, Investigation, Resources, Writing - original draft, Supervision, Project administration, Funding acquisition. **Joseph L. Baumert:** Conceptualization, Methodology, Software, Investigation, Resources, Data curation, Writing - review & editing, Supervision, Project administration, Funding acquisition. **W. Marty Blom:** Conceptualization, Investigation, Data curation, Writing - review & editing, Supervision, Project administration. **Astrid G. Kruizinga:** Conceptualization, Resources, Writing - review & editing, Project administration. **Marie Y. Meima:** Data curation, Investigation, Writing - review & editing. **Benjamin C. Remington:** Conceptualization, Writing - review & editing, Methodology, Software, Validation, Formal analysis, Investigation, Visualization, Supervision, Data curation. **Matthew W. Wheeler:** Methodology, Software, Writing - review & editing. **Joost Westerhout:** Methodology, Software, Data curation, Validation, Formal analysis, Investigation, Writing - review & editing, Visualization. **Steve L. Taylor:** Conceptualization, Resources, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Acknowledgement

This research was partly financially supported through Dutch Governmental TNO Research Cooperation Funds, the Netherlands.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.fct.2020.111831.

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