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Short Communication

Updated full range of Eliciting Dose values for Cow's milk for use in food allergen risk assessment

W. Marty Blom [a,*], Joost Westerhout [a], Joseph L. Baumert [b], Marie Y. Meima [a], Paul J. Turner [c], Motohiro Ebisawa [d], Noriyuki Yanagida [d], Benjamin C. Remington [b], Geert F. Houben [a]

[a] The Netherlands Organization for Applied Scientific Research TNO, Princetonlaan 6, 3584 CB, Utrecht, the Netherlands
[b] Food Allergy Research and Resources Program, University of Nebraska, Lincoln, Food Innovation Center, 1901 N 21 Street, PO Box 886207, USA
[c] National Heart & Lung Institute, Imperial College London, London, United Kingdom
[d] National Hospital Organization, Sagamihara National Hospital, 18-1, Sakuradai, Minami-ku Sagamihara, Kanagawa, 252-0392, Japan

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ABSTRACT

Access to Eliciting Doses (ED) for allergens enables advanced food allergen risk assessment. Previously, the full ED range for 14 allergenic foods, including milk, and recommendations for their use were provided (Houben et al., 2020). Additional food challenge studies with cow's milk-allergic patients added 247 data points to the original dataset. Using the Stacked Model Averaging statistical method for interval-censored data on the 697 individual NOAELs and LOAELs for milk generated an updated full ED distribution. The ED01 and ED05, the doses at which 1% and 5% of the milk-allergic population would be predicted to experience any objective allergic reaction, were 0.3 and 3.2 mg milk protein for the discrete and 0.4 mg and 4.3 mg milk protein for the cumulative dose distribution, respectively. These values are slightly higher but remain within the 95% confidence interval of previously published EDs. We recommend using the updated EDs for future characterization of risks of exposure of milk-allergic individuals to milk protein.

This paper contributes to the discussion on the Reference Dose for milk in the recent Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens. It will also benefit harmonization of food allergen risk assessment and risk management globally.

1. Introduction

Labeling of allergenic foods on prepacked foods is crucial in managing food allergy by the allergic population as avoidance of the allergenic food is currently still the best measure for many food allergic individuals. A list of priority allergenic foods was issued in the General Standard for the Labelling of Packaged Foods (GSLPF) in 1999, which included milk and milk products (Codex Alimentarius, 2018). This was followed by many countries and regulatory bodies implementing essential laws, regulations, or standards for labeling of "priority allergens" to provide clear labeling of priority allergens on prepackaged food products with the intent to assist allergic consumers with avoidance of their offending allergenic food source(s) (Yeung and Robert, 2018).

Despite this, cow's milk is an important cause of unexpected allergic reactions in the cow's milk-allergic population, that can be severe and even fatal (Baseggio Conrado et al., 2021; Blom et al., 2018). Cow's milk, further referred to as milk, is ubiquitous in our diet and a major source of ingredients abundantly used for the production of a variety of food products. Food allergies are acknowledged as a serious food safety issue by food industry, but pose considerable challenges for food business operators (Yeung and Robert, 2018). This is reflected in the large proportion of product recalls which involve milk or milk derivatives (Bucchini et al., 2016; Gendel, 2018). Besides issues with mislabeling products, cross-contact during production can lead to unintended allergen presence (UAP) in products. The use of precautionary allergen labeling (PAL) statements that warn consumers about possible UAP are voluntary and currently not regulated, resulting in a proliferation of different PAL on products, often unrelated to the actual risk posed to

Abbreviations: DBPCFC, double-blind, placebo controlled food challenge; ED, Eliciting Dose; FAO, Food and Agriculture Organization of the United Nations; WHO, World Health Organization; LOAEL, lowest observed adverse effect level; NOAEL, no observed adverse effect level; PAL, precautionary allergen label; RD, Reference Dose; UAP, unintended allergen presence.

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

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allergic consumers (Blom et al., 2018; DunnGalvin et al., 2019; Yeung and Robert, 2018).

Since the original drafting of the GSLPF, both allergen risk assessment and allergen management have advanced greatly (Houben et al., 2020). Reference doses (RDs) based on doses predicted to elicit objective allergic symptoms in no more than 1–5% of the allergic population have been proposed, including for milk (Houben et al., 2020; Remington et al., 2020). These RDs can be used for the calculation of Action Levels to inform the need for PAL on food products, such that PAL would only be used if the concentration of UAP is above the action level. This approach is increasingly supported by many stakeholders, including food business operators, regulatory bodies and patients' organizations (DunnGalvin et al., 2019). The full range of a population eliciting dose distribution for allergens is also valuable, allowing risk assessors to quantify the risk of an (unintended) allergen concentration in food products and support decisions with respect to allergen risk management, for instance, in incidents (explained in detail in Houben et al. (2020)).

In 2020, the Food and Agriculture Organization of the United Nations (FAO) and World Health Organization (WHO) called for experts and data on the risk assessment of food allergens based on a request from Codex Alimentarius for scientific advice (https://www.fao.org/3/ca7121en/ca7121en.pdf). Three expert meetings were held in 2020–2021 to provide scientific advice on various questions relevant to allergen management and PAL. In the second meeting, Reference Doses (called RfD by the FAO/WHO) were established using TNO-FARRP threshold datasets for major allergenic foods, on the basis that this dataset is *"the best described source available, both in terms of content and curation, with supportive peer-reviewed publications* "(FAO/WHO Expert Consultation et al., 2021). As a starting point, the Expert Consultation considered ED05 values for priority allergens, i.e., the eliciting dose predicted to result in objective reactions in no more than 5% of the allergic population for that allergen, as published in Houben et al. (2020) and Remington et al. (2020) (FAO/WHO Expert Consultation et al., 2021). For milk and sesame, experts noted that more data are now available for these allergens, which would enable a refinement of the ED05 values. Furthermore, a recent publication highlighted the need to extend the dataset for milk to provide more certainty to the ED05 for this allergen (Turner et al., 2021a). Therefore, in the present study, we sought additional eligible studies with data relating to double-blind, placebo--controlled food challenges (DBPCFC) in cow's milk-allergic individuals. Datasets meeting the strict quality criteria as published previously (Westerhout et al., 2019) were added to the existing threshold dataset (Remington et al., 2020) and a new analysis was performed using the stacked Model Averaging Method (Wheeler et al., 2021). Updated Eliciting Dose values for milk were generated for further use in allergen risk assessment and for supporting the FAO/WHO expert consultations in the decision of a Reference Dose for milk.

2. Data and methods

The dataset for milk published before in Houben et al. (2020) and Remington et al. (2020) contained 450 individual threshold data for cow's milk collected from peer-reviewed publications and unpublished clinical records. The FAO/WHO Expert Consultation identified six potential additional datasets which were subsequently investigated for availability/accessibility of individual patient data and data quality according to previously published criteria (Westerhout et al., 2019) (Supplementary Table S1). This included clear objective stopping criteria for the allergic reactions, availability of the dosing scheme (including if/when repeated doses were given), details on the challenge material, and availability of individual objective threshold doses. Where needed, authors were contacted to seek this information and address any data queries. In line with previous publications (Remington et al., 2020; Westerhout et al., 2019), only data from DBPCFCs were included, except in the case of infants and very young children where blinding was not considered necessary per established clinical consensus. The first objective symptoms of an allergic response occurring in the patient were used as the basis for the individual lowest observed adverse effect level (LOAEL), with the previous dose in the clinical protocol as the individual no observed adverse effect level (NOAEL). The doses were noted in terms of mg of total protein from the allergenic food, and were assessed in terms of discrete and cumulative doses.

For analysis of the data, interval censoring methodology was applied. Individuals were left-censored if they reacted with objective symptoms to the first challenge dose. Patients that failed to respond with objective symptoms to the uppermost challenge dose but did have a clear history of allergic reactions to milk were right-censored.

The new individual threshold data were combined with the existing dataset and analyzed with the "Stacked Model Averaging" approach developed by Wheeler et al. (2021). The R software (https://www.r-project.org/) and publicly available Stackedsurvpackage (http://doi.org/10.5281/zenodo.3401471) were used. Details of the methodology and the applied software can be found in Houben et al. (2020); Remington et al. (2020) and Wheeler et al. (2021). Briefly, the approach combines five parametric survival distributions (Weibull, Log-Gaussian (or Log-Normal), Log-Logistic, Generalized Pareto and Log-Laplace (or Log-Double-Exponential)) and assigns weights to the individual distributions based on the goodness of fit to ultimately generate a single model averaging outcome. This analysis outcome was used to determine the population Eliciting Doses for the discrete doses and cumulative doses. The method is based upon a Bayesian stacking methodology and estimates dose-to-failure based upon Markov chain Monte Carlo (MCMC) simulation. 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 the full ED range the random sampling procedure is truncated at the highest given dose (discrete or cumulative), based on all of the studies included in the dataset, as extrapolation beyond the highest given dose would lead to a change in the model average survival curve, resulting in an overestimation of lower ED values (Houben et al., 2020).

3. Results

Data were available from two studies which fulfilled the criteria (Supplementary Table S1), representing a total of 247 new individual NOAELs and LOAELs from milk allergic patients undergoing a DBPCFC: 83 from the study of Turner et al. (2021b) and 164 received from National Sagamihara Hospital reported in the publication by Yanagida et al. (2017). The population age range was under 18 years in both datasets, as is typical for cow's milk-allergy given that this food allergy typically resolves in childhood. Similar to previous studies, these new studies also included some left- and right-censored individuals. Overall, the total study population for cow's milk includes children and adults, but with young children presenting the highest proportion, with 30% of data from children aged <5 years of age, 45% aged 5–9 years, 22% aged 10–18 years and 3% > 18 year) (Supplement Fig. S1 for further detail). Supplementary Table S2 provides the updated table of Remington et al. (2020) for the sources of data points for milk along with the number of right- or left-censored subjects, geographic location, first mg protein dose in the food challenge protocol, and the number of children or adults. In total, 697 data points were available to model the Eliciting Dose distribution. Fig. 1 displays as the Stacked Model Averaging result with the individual distributions. Overall, the weights given to the individual models were similar to the previous milk dataset (Houben et al., 2020; Remington et al., 2020), with a high weight to the Weibull model followed by the Log-Laplace (Log-Double-Exponential) model. A slightly higher weight was observed for the Log-Laplace (Log-Double-Exponential) model for the updated dataset; however, most of the weight was still given to the Weibull model. The accompanying weighing results for the individual models are presented in Supplementary Table S3.

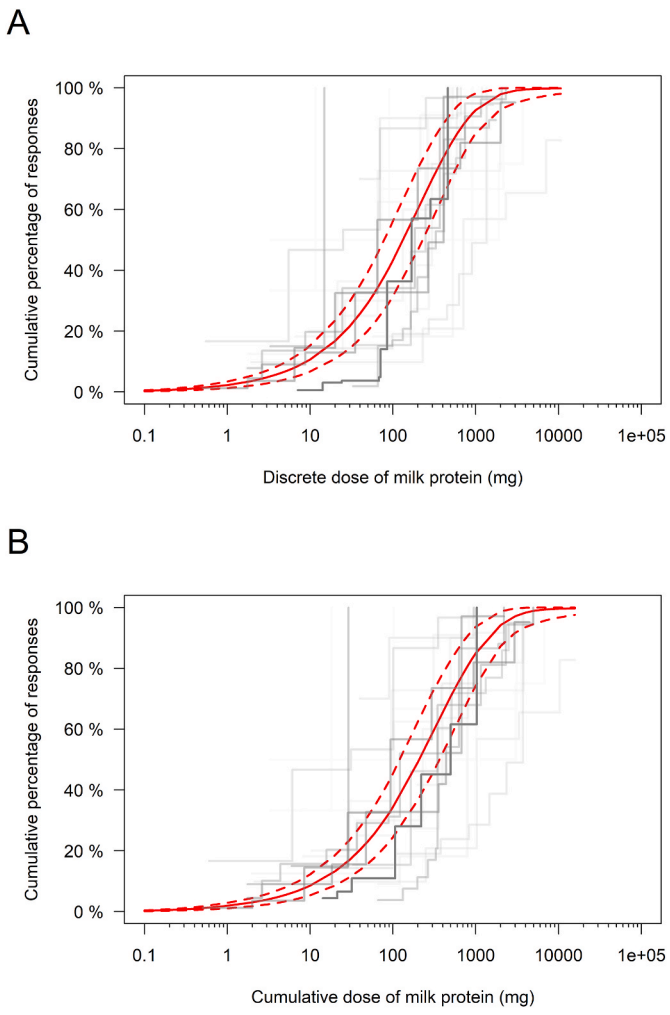

Fig. 1. Dose distribution modeling for cow's milk expressed as discrete dose (A) or the cumulative dose (B) of mg milk protein.

The 55% increase of the total size of the milk dataset resulted in small increases of the ED values compared to the previously published data on the ED01 and ED05 (Remington et al., 2020) and the full range distribution for milk (Houben et al., 2020). Table 1 provides updated EDs up to the ED50, while Supplementary Table S4 provides the full updated ED range for milk for use in allergen risk assessment to determine the risk of (unintended) concentrations of milk protein in food products.

Table 1
The ED01 to ED10, ED15, ED20, ED25, and ED50 values from the model averaged population threshold dose distributions for cow's milk (n = 697), 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).

A. Discrete dose dataset				B. Cumulative dose dataset			
ED	mg[a)]	LCI	UCI	ED	mg[a)]	LCI	UCI
ED01.0	**0.3**	**0.2**	**0.7**	**ED01.0**	**0.4**	**0.3**	**0.9**
ED02.0	0.8	0.5	1.8	ED02.0	1.1	0.6	2.4
ED03.0	1.5	0.8	3.1	ED03.0	2.0	1.0	4.3
ED04.0	2.3	1.3	4.7	ED04.0	3.1	1.7	6.5
ED05.0	**3.2**	**1.8**	**6.4**	**ED05.0**	**4.3**	**2.4**	**9.0**
ED06.0	4.2	2.3	8.3	ED06.0	5.8	3.2	11.8
ED07.0	5.2	3.0	10.3	ED07.0	7.3	4.0	14.8
ED08.0	6.4	3.6	12.4	ED08.0	9.0	5.0	18.0
ED09.0	7.6	4.4	14.7	ED09.0	10.8	6.0	21.5
ED10.0	9.0	5.1	17.1	ED10.0	12.8	7.1	25.1
ED15.0	16.7	9.7	31.0	ED15.0	24.3	13.8	46.3
ED20.0	26.3	15.5	47.8	ED20.0	39.0	22.4	72.5
ED25.0	37.9	22.4	67.7	ED25.0	56.8	32.8	104
ED50.0	133	79.3	229	ED50.0	207	120	364

[a] ED values are expressed in mg total milk protein.

The Bayesian Stacked Parametric Survival methods with Frailty Components and Interval Censored Failure Times as described by Wheeler et al. (2021) were used. In this Stacked Model Averaging technique, five different parametric distributions are modelled, weighted and combined into a single dose distribution estimate in order to maximize the predictive accuracy of the calculated ED values. The predicted Stacked Model Averaging distribution estimate (red line) is presented with its corresponding 95% posterior predicted failure times (dashed red lines). The Kaplan-Meier curves for each individual study in the dataset are also presented (black lines, darker shades indicate studies with more observations).

Both ED01 and ED05 values have previously been considered in the framework of establishing Reference Doses for allergen management and the calculation of action levels (FAO/WHO Expert Consultation et al., 2021). The updated ED01 and ED05 values were in the same range as the previously reported values and with overlapping 95% confidence intervals (Table 2). The effect of including the additional data to the milk distributions was small (Fig. 2), though the small change in weighing of the various parametric survival models, with a higher weight to the Log-Laplace(Log-Double-Exponential) model for the updated dataset (Supplementary Fig. S2), resulted in a slightly larger confidence interval in the lower and higher ends of the curve for the updated milk dose distribution (Table 2 and Fig. 2) compared to the dataset of Houben et al. (2020).

We also undertook a sensitivity analysis including data from Rolinck-Werninghaus et al. (2012). These data were omitted from the final analysis because of uncertainties regarding whether specific challenges were undertaken using DBPCFC or not. As previously published, a DBPCFC procedure is one of our quality criteria for addition of data to our database and analysis, with exception of data for the youngest children (Westerhout et al., 2019). In addition, individual symptom data was not available, so it was unclear as to whether some of the threshold doses met the criteria outlined in Westerhout et al. (2019). However, given the size of this dataset, we evaluated the possible effect of the inclusion of these additional data on the ED values. For this sub-analysis, including the data from Rolinck-Werninghaus et al. (2012), there were a total of 1002 data points, resulting in an ED01 of 0.2 mg (95% CI 0.1–0.3) of total milk protein and an ED05 of 2.1 mg (95% CI 1.2–3.8) of total milk protein for the discrete dose distribution. For the cumulative dose distribution, the estimated ED01 was 0.3 mg (95% CI 0.2–0.5), and the ED05 was 2.9 mg (95% CI 1.6–5.4) of total milk protein. Therefore, the inclusion of data from Rolinck-Werninghaus et al. (2012) resulted in slightly lower estimates for ED01 and ED05, but the resulting ED01 and ED05 values were almost equal to those presented in Remington et al. (2020) and (Houben et al. (2020) (Supplementary Fig. S3).

4. Discussion

Population EDs values are valuable for use in allergen risk assessment and for the derivation of reference doses to inform the decision for the use of PAL. Milk protein is an important cause of accidental allergic reactions due to unintended presence in food products with or without a PAL statement (Blom et al., 2018). Milk is also a major cause of anaphylaxis and even death globally (reviewed by Baseggio Conrado et al. (2021). An internationally-harmonized Reference Dose to inform the decision to either or not apply a PAL statement, as proposed by the FAO/WHO expert consultation (FAO/WHO Expert Consultation et al., 2021), would represent a step forwards in improving allergen risk management with respect to cow's milk, and importantly, offer safer food choices for allergic consumers.

The addition of 247 new data points from DBPCFC in cow's milk-

Table 2
Comparison of the updated ED01 and ED05 for cow's milk with the previously reported EDs. The ED values are expressed in mg total milk protein, along with the 95% confidence interval (95% CI).

		Discrete		Cumulative	
Dataset	No of individuals	ED01 (95% CI)	ED05 (95% CI)	ED01 (95% CI)	ED05 (95% CI)
Updated milk ED distribution	697	0.3 (0.2–0.7)	3.2 (1.8–6.4)	0.4 (0.3–0.9)	4.3 (2.4–9.0)
Milk ED distribution (Houben et al., 2020)	450	0.2 (0.1–0.5)	2.4 (1.3–5.0)	0.3 (0.2–0.6)	3.1 (1.6–6.6)

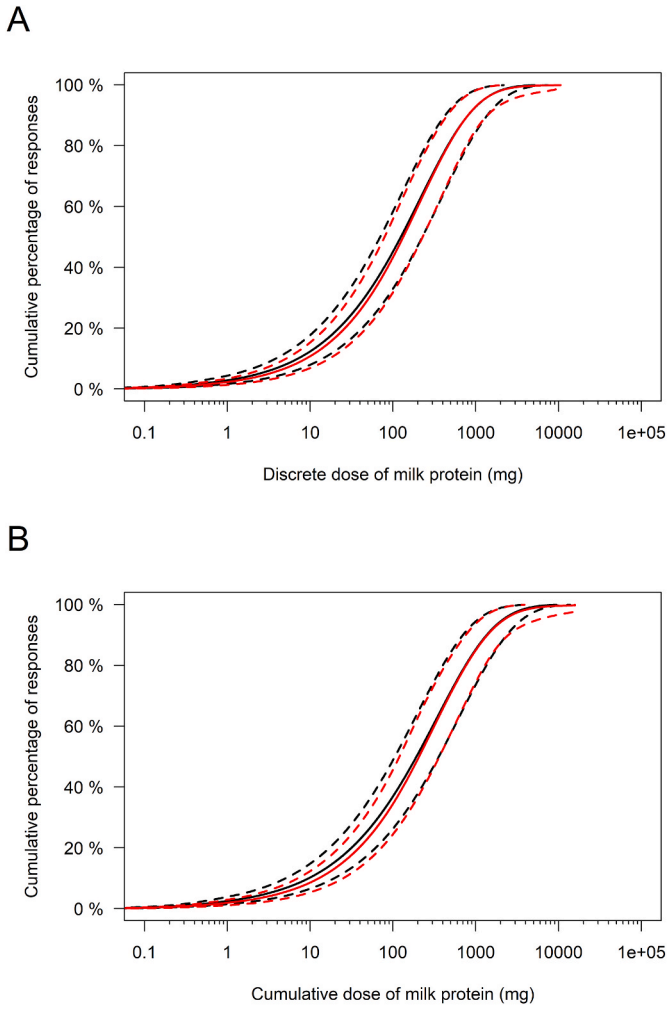

Fig. 2. ED curves from the model average population threshold dose distribution for milk (Houben et al., 2020) (black) and the updated milk distribution with the 95% confidence interval (red). (A) Discrete and (B) Cumulative dose dataset. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

allergic patients to the existing TNO-FARRP dataset for milk (n = 450) did not result in significantly different ED01 and ED05 values, or in a significant shift in the overall population ED distribution for milk-allergic individuals. Previous research predicted that expansions of already large datasets used to calculate EDs will unlikely result in significant changes in the EDs (Klein Entink et al., 2014; Remington et al., 2020). A factor that may contribute to the small variation in modelling results of the final EDs can be the use of a protocol starting at relatively higher doses, such as with the study of Yanagida et al. (2017). In our current analysis, addition of the two new datasets resulted in a small difference in the weighing of the models, which slightly changed the lower and higher end of the modelled distributions and caused a slightly larger confidence interval despite the larger number of datapoints. This is the result of the type of datasets added. The sensitivity analysis showed that adding the dataset of Rolinck-Werninghaus et al. (2012), reduced the confidence interval. With every new dataset added, there will be some change in the exact ED values and confidence intervals, but our present analysis shows that, overall, the population ED distribution for milk remains stable. The small variability would be predicted to have no relevant effect for the estimation of the risk of allergen levels in food products. The addition of the dataset of Rolinck-Werninghaus et al. (2012) in our sub-analysis shifted the discrete ED05 back to 2.1 mg milk protein, very close to the discrete ED05 value of 2.4 mg milk protein published previously (Houben et al., 2020; Remington et al., 2020), but all EDs remained within the 95% confidence interval of the updated and the previously published population ED distribution (Houben et al., 2020).

The present study was limited to including just two additional studies, though a substantial number of new data points were added. Additional food challenges – both DBPCFC and open challenges to cow's milk – have been reported elsewhere both in publications and unpublished data, but these studies did not meet our quality criteria (Westerhout et al., 2019) or individual challenge data were not available for inclusion. To avoid confusion and potentially small differences in calculated risks among risk assessors and managers worldwide, updating any threshold dose distribution should have a clear rationale. For example, if uncertainty can be reduced through the inclusion of new datapoints.

Various ED05 values have been published for milk in different studies, varying in value depending on the dataset (size, possible patient selection, dosing scheme) and methodology used to model the data for estimating an ED value (in mg milk protein) used (Klein-Entink et al., 2014; Remington et al., 2020; Wheeler et al., 2021). As indicated by Turner et al. (2021a), these ED05 estimates can vary from 0.5 to 13.9 mg milk protein.

A single-dose challenge study recently queried whether the previous ED05 estimates for milk might be an overestimate (Turner et al., 2021a), a concern also raised by Rolinck-Werninghaus et al. (2012). The single dose study with milk by Turner et al., (2021a) investigated the reaction frequency at a dose of 0.5 mg milk protein in a population of 172 milk allergic patients. The reaction frequency found in the study indicated that the 0.5 mg dose tested might comply with an ED05, but could reflect an ED value between ED3.7 to ED11.9. According to the data published by Houben et al. (2020) a 0.5 mg dose of milk protein would reflect an ED value between the ED0.9 and ED3.0, based on the confidence intervals of the discrete and cumulative dose distribution datasets. Turner et al., (2021a) suggested that additional, larger challenge data sets are needed to provide more precision to the population dose-distribution modelling around lower ED values. Our current study provides such dataset extension by incorporating additional data, which included participants from Turner et al. (2021a), as well as sensitivity analysis on including even more datapoints to the existing large milk threshold dataset. This sensitivity analysis included data from Rolinck-Werninghaus et al. (2012). Based on the confidence intervals of the extended discrete and cumulative dose distribution datasets (see Supplementary

Table S4), a 0.5 mg dose of milk protein reflects an ED value between ED0.8 and ED2.0 and indeed shows a more narrow interval and thus higher precision compared to the ED-estimate of a 0.5 mg dose based on Houben et al., (2020). Both Houben et al., 2020 and our current study indicate a slightly lower ED value for the 0.5 mg dose compared to the results of Turner et al., (2021a). This might well be associated with the substantial smaller dataset used by Turner et al., (2021a) and possibly an associated different range and variability in patient sensitivity, but also with the study conduct. The single-dose challenge study conducted by Turner et al., (2021a) aimed to test whether a dose of 0.5 mg milk protein could comply with an ED05 and did not falsify this hypothesis, as any outcome between an ED3.7 and ED11.9 confirmed the hypothesis. It should be noted however that such study using only one single dose is not suitable to model eliciting dose distributions and estimate ED values. For the latter purpose, full eliciting dose distributions based on multiple dose levels as presented in our current study are needed.

Our study showed that additions of new data to the already large dataset used by Houben et al. (2020) only marginally changed the population ED values and provided assurance that the ED-estimates from our dataset are robust. The overall dataset has a broad age-distribution and the results of this study gives assurance that the estimated ED01 and ED05 for milk generated in this and our previous study (Houben et al., 2020) are sufficiently robust for use in risk assessment and management decisions for the (unintended) presence of milk protein in food products.

The present study provides the updated full range of ED values for milk protein (Supplementary Table S4) that we now recommend to use for risk assessment and management purposes. For other priority allergenic foods, readers are referred to the original publications of Houben et al. (2020) and Remington et al. (2020).

CRediT authorship contribution statement

W. Marty Blom: Conceptualization, Methodology, Investigation, Resources, Visualization, Writing – original draft, Data curation, Supervision, Project administration, Funding acquisition. **Joost Westerhout:** Methodology, Software, Data curation, Validation, Formal analysis, Investigation, Visualization, Writing – review & editing. **Joseph L. Baumert:** Conceptualization, Methodology, Investigation, Resources, Data curation, Writing – review & editing, Supervision, Project administration, Funding acquisition. **Marie Y. Meima:** Data curation, Investigation, Writing – review & editing. **Paul J. Turner:** Conceptualization, Formal analysis, Investigation, Data curation, Writing – review & editing. **Motohiro Ebisawa:** Investigation, Formal analysis, Data curation, Writing – review & editing. **Noriyuki Yanagida:** Investigation, Formal analysis, Data curation, Writing – review & editing. **Benjamin C. Remington:** Conceptualization, Methodology, Validation, Investigation, Data curation, Writing – review & editing. **Geert F. Houben:** Conceptualization, Investigation, Data curation, Writing – review & editing, Supervision, 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.

Data availability

The data used for the research is a mixture of publicly available data and confidential data for which the authors do not have permission to share the data

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Appendix A. Supplementary data

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