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## MEETING REPORT



# RISK ASSESSMENT OF FOOD ALLERGENS

PART 5: REVIEW AND ESTABLISH THRESHOLD LEVELS FOR SPECIFIC TREE NUTS (BRAZIL NUT, MACADAMIA NUT OR QUEENSLAND NUT, PINE NUT), SOY, CELERY, LUPIN, MUSTARD, BUCKWHEAT AND OATS



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MUSTARD, BUCKWHEAT AND OATS

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# CONTENTS

Contributors.....	v
Acknowledgements.....	vii
Abbreviations .....	viii
Declarations of interests .....	ix

## CHAPTER 1

<b>CODEx COMMITTEE ON FOOD LABELLING (CCFL) REQUEST.....</b>	<b>1</b>
--	----------

## CHAPTER 2

<b>SAFETY OBJECTIVE.....</b>	<b>3</b>
------------------------------	----------

## CHAPTER 3

<b>WAYS OF WORKING.....</b>	<b>5</b>
-----------------------------	----------

## CHAPTER 4

<b>RESULTS.....</b>	<b>7</b>
---------------------	----------

<b>REFERENCES.....</b>	<b>9</b>
------------------------	----------

## ANNEXES

<b>ANNEX 1. ....</b>	<b>11</b>
----------------------	-----------

A1.1 Description of guidelines used for deriving reference dose (RfD) recommendations from ED05 values in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens...	11
--	----

A1.2 Specific Tree nuts .....	12
-------------------------------	----

A1.2.1 Brazil nuts .....	12
--------------------------	----

A1.2.2 Macadamia nuts (Queensland nuts) and Pine nuts.....	13
--	----

A1.3 Soy .....	14
----------------	----

A1.4 Celery/celeriac.....	16
---------------------------	----

A1.5 Lupin.....	17
-----------------	----

A1.6 Mustard .....	19
--------------------	----

A1.7 Buckwheat.....	21
---------------------	----

A1.8 Oats .....	23
-----------------	----

<b>ANNEX 2. ....</b>	<b>25</b>
----------------------	-----------

<b>ANNEX 3. ....</b>	<b>26</b>
----------------------	-----------

<b>REFERENCES IN ANNEX.....</b>	<b>29</b>
---------------------------------	-----------

## TABLES

1	Consensus reference dose (RfD) recommendations and potential “values for risk management” .....	7
A1	Studies reporting food challenges to buckwheat.....	26
A2	ED <sub>01</sub> to ED <sub>10</sub> values from the model averaged population threshold dose distributions for buckwheat, based on discrete and cumulative dose datasets. ED values are expressed in mg total buckwheat protein. The 95% confidence interval is represented by the lower confidence interval (LCI) and the upper confidence interval (UCI) .....	28

## FIGURES

A1	Families of specific tree nuts and other selected allergenic foods on the phylogenetic tree .....	25
A2	Dose distribution modelling utilizing Bayesian stacked model averaging methodology for buckwheat, based on discrete (upper graph) and cumulative (lower graph) dose datasets. Doses are expressed as mg buckwheat protein. The predicted dose 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 (grey lines, darker indicates study with more observations). .....	27

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The preparatory work and the convening of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens required to generate this report was coordinated by the Secretariat.

Appreciation is also extended to all those who responded to the Call for Data that was issued by FAO and WHO and provided relevant reports and references. FAO and WHO would also like to acknowledge the financial resources provided by Canada to support this work.

## ABBREVIATIONS

<b>CAC</b>	Codex Alimentarius Commission
<b>CCFH</b>	Codex Committee on Food Hygiene
<b>CCFL</b>	Codex Committee on Food Labelling
<b>CI</b>	confidence interval
<b>ED<sub>p</sub></b>	the eliciting dose predicted to provoke reactions in a specified percentage (p) of the allergic population
<b>ED<sub>01</sub></b>	the eliciting dose predicted to provoke reactions in 1% of the allergic population
<b>ED<sub>05</sub></b>	the eliciting dose predicted to provoke reactions in 5% of the allergic population
<b>ED<sub>10</sub></b>	the eliciting dose predicted to provoke reactions in 10% of the allergic population
<b>ED<sub>15</sub></b>	the eliciting dose predicted to provoke reactions in 15% of the allergic population
<b>ED<sub>50</sub></b>	the eliciting dose predicted to provoke reactions in 50% of the allergic population
<b>ELISA</b>	enzyme-linked immunosorbent assay
<b>FAO</b>	Food and Agriculture Organization of the United Nations
<b>IgE</b>	immunoglobulin E
<b>MED</b>	minimum eliciting dose
<b>RA</b>	risk assessment
<b>RfD</b>	reference dose
<b>TNO</b>	Netherlands Organisation for Applied Scientific Research
<b>VITAL®</b>	Voluntary Incidental Trace Allergen Labelling
<b>WHO</b>	World Health Organization

## DECLARATIONS OF INTERESTS

All participants completed a Declaration of Interests form in advance of the meeting. Three of the participants declared interest in the topic under consideration. Markus Lacorn and Eva Södergren declared significant interests connected with their employment, and Clare Mills declared interests connected to investments that exceeded FAO/WHO's threshold. It could not be excluded that the declared interests may be perceived as a potential conflict of interest. Therefore, while all three persons mentioned above had been invited to participate in the meeting, they had been excluded from the decision-making process regarding final recommendations and participated only as technical resource people.

All remaining experts were not considered by FAO and WHO to have declared any interest that may be perceived as a potential conflict with regard to the objectives of the meeting.

All the declarations, together with any updates, were made known and available to all the participants at the beginning of the meeting.

All the experts participated in their individual capacities and not as representatives of their countries, governments or organizations.



# CHAPTER 1

---

## CODEX COMMITTEE ON FOOD LABELLING (CCFL) REQUEST

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In Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b), reference doses (RfDs) were recommended for the global priority allergens (FAO and WHO, 2022a), which included: walnut (and pecan), cashew (and pistachio), almond, peanut, egg, hazelnut, wheat, fish, shrimp, milk, and sesame. Still, RfDs were not recommended for a number of regional or national priority allergens as they did not meet the criteria to be global priority allergens.

In an additional request, the Codex Committee on Food Labelling (CCFL) indicated interest in potential RfD derivation for the following specific food allergens: specific tree nuts (Brazil nut, macadamia nut or Queensland nut, pine nut), soy, celery, lupin, mustard, buckwheat, and oats.

These specific foods were not recommended as global priority allergenic foods by the Expert Committee during Part 1 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022a) and were thus not subject to discussion during Part 2 (FAO and WHO, 2022b) when RfDs were derived for global priority allergenic foods.

An overview of the available data and recommended RfDs (or reasons no RfD could be derived) are given here for these specific food allergens. These RfDs were derived following the guidelines described in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation (FAO and WHO, 2022b) for deriving an RfD for priority allergenic foods. Details of the available data and discussions of the Expert Committee are presented in Annex 1.



# CHAPTER 2

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## SAFETY OBJECTIVE

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The Expert Committee reiterated that the safety objective underlying the definition of RfDs remained the same as elaborated in the second meeting, i.e.:

to minimise the probability of any clinically relevant objective allergic response, (as defined by dose-distribution modelling of minimum eliciting doses [MEDs]) to a point where further refinement does not meaningfully reduce public health impact (FAO and WHO, 2022b, p. 11).





# CHAPTER 3

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## WAYS OF WORKING

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A summary of the available data for each allergenic food in the CCFL request was prepared, together with proposed reference dose(s) as described in Chapter 1 and shared with members of the Expert Committee prior to an online meeting. Members of the Expert Committee were also sent a questionnaire in which they were invited to select their choice(s) of RfD or to object to any of the choices. They were also requested to indicate the reasons for their choice(s) and share any further comments. For any allergen, respondents were allowed to propose more than one response. Responses were summarized and presented to the meeting for discussion and conclusion.

Reference doses (RfDs) are health-based guidance values which allow for the management of the risk from specific allergens. A guiding principle for the discussions was that risk management is best served if RfDs are defined for any given allergen, where the data permit, even if all adequacy criteria are not fully met.

A potential “value for risk management” was discussed and proposed when it was not possible, from a scientific rationale (i.e. data were too limited quantitatively or potentially of too limited quality, or both), to provide an RfD for a specific food following the guidelines described in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation.



# CHAPTER 4

## RESULTS

The table below summarizes the initial (pre-meeting) questionnaire results and final outcomes for each of the allergenic foods in the Codex CCFL request.

TABLE 1 **CONSENSUS REFERENCE DOSE (RFD) RECOMMENDATIONS AND POTENTIAL “VALUES FOR RISK MANAGEMENT”**

ALLERGENIC FOOD	INITIAL ASSESSMENT INCLUDING RFD (questionnaire results) (number of committee members agreeing with this option/total number)	FINAL RECOMMENDATION (mg total protein from the allergenic source)	REMARKS
Celery/celeriac	Consensus (19/19) for 1 mg RfD	1	<b>Final RfD</b> <ul style="list-style-type: none"> <li>Derived following Report 2 guidelines and based on lowest ED<sub>05</sub> of 1.3 mg (Remington <i>et al.</i> [2020]; Houben <i>et al.</i> [2020])</li> <li>Severity of reactions and hidden presence warrants alignment with lowest RfD</li> </ul>
Soy	Consensus (19/19) for 10 mg RfD	10	<b>Final RfD</b> <ul style="list-style-type: none"> <li>Derived following Report 2 guidelines and based on lowest ED<sub>05</sub> of 10 mg (Remington <i>et al.</i> [2020]; Houben <i>et al.</i> [2020])</li> <li>Consistent with low severity profile</li> </ul>
Brazil nuts	15/19 1 mg 0/19 3 mg 4/10 neither 1 mg nor 3 mg	1	<b>Value for risk management</b> <ul style="list-style-type: none"> <li>Not scientifically possible to derive formal RfD for any of the nuts: no data</li> <li>Similar conservatism as that applied to almond in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation</li> </ul>
Macadamia (Queensland) nuts			
Pine nuts			
Mustard	9/19 no RfD 7/19 0.5 mg 1/19 1 mg 1/19 0.1 mg 1/19 all options valid	1	<b>Value for risk management</b> <ul style="list-style-type: none"> <li>Not scientifically possible to derive formal RfD: inadequate data</li> <li>Recognizes severity profile of mustard reactions (high) and low ED values (Remington <i>et al.</i> [2020]; Houben <i>et al.</i> [2020])</li> </ul>
Lupin	9/19 no RfD 6/19 15 mg 3/19 other RfD 1/19 all options valid	10	<b>Value for risk management</b> <ul style="list-style-type: none"> <li>Not scientifically possible to derive formal RfD in view of poor data quality</li> <li>Severity of reactions similar to soy and ED values in same range as for soy (Remington <i>et al.</i> [2020]; Houben <i>et al.</i> [2020])</li> </ul>
Buckwheat	12/19 no RfD 5/19 10 mg 1/19 10 mg or no RfD 0/19 15 mg	10	<b>Value for risk management</b> <ul style="list-style-type: none"> <li>Not scientifically possible to derive formal RfD in view of very limited data and poor data quality</li> <li>Severity of reactions similar to soy</li> </ul>
Oats	Consensus (19/19) for no RfD	Oat-specific RfD not appropriate	IgE-mediated food allergy risks identified for oats stem from cross contact with other grains in oats rather from oats themselves. An oat-specific RfD would be an inappropriate way of managing this issue and constitute misuse of a valuable risk management tool. See Reports 2 & 3 for RfDs and cross contact risk assessment support regarding other grains (or other priority allergenic foods) in oats (FAO and WHO, 2022b, 2023).

*Note:* Ordered to separate the foods with consensus and final RfD recommendations from those with values for risk management for clarity.

The Expert Committee highlighted the need for additional clinical research for Brazil nut, macadamia nut, pine nut, mustard, lupin, and buckwheat and emphasized that the use of any values for risk management for these foods should not be a reason to stop or delay such research.

The Expert Committee reiterated the importance of assessing and developing analytical method capabilities in relation to the recommended RfDs and risk management values. The committee observed that some RfDs can be implemented and monitored to some degree with current analytical capabilities but acknowledged that significant limitations on method performance exist, coupled with a lack of methods for many of the allergenic foods. They further strongly repeated the recommendation in Report 2 that the expression of analytical results be standardized as milligram (mg) total protein of the allergenic food per kilogram (kg) of food product analysed in order to facilitate interpretation of results by users of analytical services. To address deficiencies in analytical methodology, they recommended the development of method performance criteria, as well as a more extensive provision of accessible reference materials for the allergenic foods encompassed by the request for which RfDs or risk management values were recommended.

As was the case with global priority allergens, the Expert Committee also identified the need for better understanding of assay performance in different food matrices and greater transparency over assay-specific reagents, such as antibodies used in enzyme-linked immunosorbent assays (ELISA), which are critical to assay performance. Other areas identified for improvement include defined procedures for obtaining samples for analysis and for curation of samples for third party analytical laboratories.

The Expert Committee also reiterated its previous advice that analytical testing and associated issues should be reviewed by the Codex Committee on Methods of Analysis and Sampling (CCMAS).

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# ANNEX 1

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## **A1.1 DESCRIPTION OF GUIDELINES USED FOR DERIVING REFERENCE DOSE (RfD) RECOMMENDATIONS FROM ED<sub>05</sub> VALUES IN PART 2 OF THE AD HOC JOINT FAO/WHO EXPERT CONSULTATION ON RISK ASSESSMENT OF FOOD ALLERGENS**

Report 2 states:

Having debated these issues, the expert committee opted for a simplification process. In the first instance, for most allergens, the actual ED<sub>05</sub> values on which the RfDs are based were rounded down to a single significant figure on the basis of the size of the confidence intervals. Exceptions were those allergens for which the data were susceptible to a high degree of bias (e.g. cashew, walnut) or where there could be a high degree of uncertainty about the true value of the ED<sub>05</sub> due to the limited number of species tested within a food group (e.g. fish, shrimp/crustacea). Due to these uncertainties, fish and shrimp/crustacea ED<sub>05</sub> values were rounded down further than the other foods (FAO and WHO, 2022b, pp. 89–90).

The resulting RfD values were then collated into different ranges and further simplified within the ranges, using the same principle of rounding down (FAO and WHO, 2022b, p. 90).

Furthermore, the report describes the safety objective:

"the experts agreed that the safety objective addressed by RfD should be to:

minimise the probability of any clinically relevant objective allergic response, (as defined by dose-distribution modelling of minimum eliciting doses [MEDs]) to a point where further refinement does not meaningfully reduce public health impact.

This should be supported by data demonstrating that incidental symptoms likely to be elicited in the range of envisioned RfDs are of an acceptable severity" (FAO and WHO, 2022b, p. 11).

The principles and approach described in Report 2 were thus followed in responding to the request by CCFL.

In this Annex, data for dose-distribution modelling for individual foods are detailed in a similar fashion to that in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation, with information provided for each regarding:

- > Available/accessible studies
- > Quality/quantity
- > Recommendation

## A1.2 SPECIFIC TREE NUTS

### A1.2.1 BRAZIL NUTS

During the potency review in Part 1 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens, no potency data were identified for Brazil nuts (FAO and WHO, 2022a), and consequently there were insufficient data for dose-distribution modelling. This lack of data on Brazil nuts is shared by other tree nuts, which were identified as global priority allergens, including almond, pecan and pistachio, for which reference doses were recommended in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b).

Similar to many other tree nuts, Brazil nut was found to have a “higher proportion of anaphylaxis” in 3+ CODEX regions (Brazil nut – Level 2 evidence; other tree nuts – Level 3 evidence) (FAO and WHO, 2022a, p. 58), and further review of data regarding expected rates of anaphylaxis at low-dose exposures found no evidence that Brazil nut differs from other tree nuts (Turner *et al.*, 2022).

Almond similarly lacked potency data but had similar severity data to that available for Brazil nut. It was treated conservatively during Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b) and was grouped at an RfD of 1 mg total protein from the allergenic source along with cashew/pistachio and walnut/pecan, rather than with hazelnut at 3 mg total protein from the allergenic source.

In discussion, the Expert Committee noted that phylogenetic relationships were unhelpful in reaching a decision, Brazil nut being phylogenetically somewhat distant from other tree nuts – see Appendix 2 (The Angiosperm Phylogeny Group, 2016). The group also observed that it is scientifically not possible to set an RfD for Brazil nut from a *risk assessment* perspective, but on a precautionary basis, a provisional RfD of 1 mg aligning with almond would fit from a *risk management* perspective. The group also cautioned that potential drawbacks needed to be acknowledged, including limiting future research into MEDs (individual threshold data) for this allergenic food. However, they agreed that setting an RfD was helpful in relation to allergen management and public health, but the recommendation should stress the limitations of the data and could be changed if and when adequate data emerge.

#### Recommendation

A similar conservatism as that applied in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation leads to a recommended value for risk management for Brazil nut of 1 mg total protein from the allergenic source based on grouping with other tree nuts (cashew/pistachio, walnut/pecan, almond, macadamia nuts [Queensland nuts], and pine nuts). The Expert Committee underlined that this recommendation is not based on a risk assessment but should be considered a value for risk management purposes, given that the values are not based on data for the actual allergenic food and are therefore subject to change if and when adequate data emerge.



### A1.2.2 MACADAMIA NUTS (QUEENSLAND NUTS) AND PINE NUTS

During the potency review in Part 1 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens, no potency data were identified for macadamia nuts (Queensland nuts) or pine nuts (FAO and WHO, 2022a) and consequently there were insufficient data for dose-distribution modelling. Still, this lack of data is shared by several other tree nuts such as almond, pecan and pistachio, for which reference doses were recommended in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b).

In contrast to other tree nuts, macadamia nut and pine nut were found to have a “higher proportion of anaphylaxis” in 1–2 CODEX regions (Level 2 evidence) instead of the 3+ CODEX regions (Level 1 evidence) seen for other tree nuts (FAO and WHO, 2022a, p. 58). Again, further review of data regarding expected rates of anaphylaxis at low-dose exposures found no evidence that macadamia nut would show a pattern of greater severity than other tree nuts, while no data were available for pine nuts (Turner *et al.*, 2022).

As discussed in the review on Brazil nut, almond similarly lacked potency data but had stronger severity data available than that available for macadamia nut, and was treated conservatively during Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b), finally being grouped at an RfD of 1 mg total protein from the allergenic source along with cashew/pistachio and walnut/pecan, rather than hazelnut at 3 mg total protein from the allergenic source. The Expert Committee discussed macadamia nut and pine nuts together with Brazil nut, and the comments made and reservations expressed in relation to the Brazil nut provisional RfD apply equally to macadamia and pine nuts, and indeed even more strongly with regard to phylogenetic relationships, as macadamia is even more distant from other tree nuts than Brazil nuts, while pine nut belongs to a different clade (gymnosperms rather than angiosperms).

#### Recommendation

A similar conservatism to that in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation leads to a recommended value for risk management for macadamia nut (Queensland nuts) and pine nuts of 1 mg total protein from the allergenic source to be grouped with other tree nuts (cashew/pistachio, walnut/pecan, almond, and Brazil nut). The Expert Committee underlined that this recommendation is not based on a risk assessment but should be considered as values for risk management purposes, given that the values are not based on data for the actual allergenic foods and are therefore subject to change if and when adequate data emerge.

## A1.3 SOY

The Expert Committee recently concluded that soy does not meet the criteria set for a global priority allergen on the basis of low prevalence and potency, as well as on globally rare reports of anaphylaxis (FAO and WHO, 2022a). However, data are available to derive an RfD for soy, and as it is a priority allergenic food in many countries, an RfD would help science-based allergen management.

### Available and accessible studies

As detailed in the supplementary information from Remington *et al.* (2020), there are nine studies available for soy (five from published literature and four unpublished clinical datasets) with a total of 87 individuals included in the analysis (six left-censored, 33 right-censored); 28 identified as adults, and 37 identified as children.

### Quality and quantity

In Part 1 of this Ad hoc Joint FAO/WHO Expert Consultation, analysis of the potency data from Remington *et al.* (2020) and Houben *et al.* (2020) showed an adequate quantity of data available for dose-distribution modelling (n = 87) and a high potential for biases with the available data for soy. The amount of available potency data for soy was similar to that for celery/celeriac (n = 82 data points), fish (n = 82 data points), shrimp (n = 75 data points), walnut (n = 74 data points), and wheat (n = 99 data points).

The high potential for biases<sup>1</sup> in the available data for soy was attributed to available data being from Europe and North America only (i.e. two Codex regions) with more than a third of the data being right- or left-censored (FAO and WHO, 2022a). Additionally, it was noted that a high percentage (40 percent) of the available soy data were from unpublished sources.

Among the 87 clinical data points, six were left-censored and 33 right-censored (corresponding to 38 percent of the dataset) (Remington *et al.*, 2020). Data were available from 54 individuals challenged with soy flour/infant formula and for 33 individuals challenged with soy milk (Taylor *et al.*, 2021).

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<sup>1</sup> Excerpt from FAO and WHO, 2022a, p. 39: Assessment of bias, “We attempted to provide a qualitative estimate of whether the EDP estimates could be biased, starting from the goal of identifying global priority allergenic foods and ingredients. Thus, studies limited to a small number of regions, or even confined to limited parts of wider regions (e.g. data from celery studies being confined to Central Europe) would lead to a conclusion of potentially high bias. Other factors included whether studies were limited to a particular fraction of the population (e.g. children) or where inclusion criteria could plausibly have led to a more (or less) sensitive population being tested (e.g. immunotherapy studies). Finally, factors inherent in the study design or results which could affect the shape of dose-distributions, such as a high proportion of left- or right-censored results, also contributed to our overall judgement.”

While patterns of clinical reactivity to certain forms of soy may vary between individuals with soy allergy, in a review of currently available data, Taylor *et al.* (2021) found that:

the potency of soy milk is not different from soy flour and soy-based infant formula. While, with the currently available data, no evidence exists to conclude that soy milk responders as a whole group display a relevantly different ED-distribution, more clinical research would reduce the statistical uncertainties associated with the soy milk and soy flour distribution (Taylor *et al.*, 2021, p. 107).

Results from the analysis with the combined soy flour/infant formula and soy milk datasets are summarized here.

The eliciting dose predicted to provoke reactions in 5 percent of the allergic population (ED<sub>05</sub>) of the discrete dosing scheme was established at 10.0 mg protein (CI 95 percent: 2.2, 54.6) with the Bayesian stacked model averaging methodology and the ED<sub>05</sub> of the cumulative dosing scheme was established at 14.1 mg protein (CI 95 percent: 3.1, 76.2) (Remington *et al.*, 2020). Relatively large confidence intervals (CIs) for both ED<sub>05</sub>s can be partially attributed to the high proportion of right-censored data. There is no single-dose challenge study available to verify the ED<sub>05</sub> for soy in an unselected outpatient clinic population.

Soy was also determined to belong to the lowest grouping for severity (Group C [I] – Level 1 evidence – Lower proportion of anaphylaxis, all regions) (FAO and WHO, 2022a). Thus, soy had the lowest expected rate of anaphylaxis in response to an allergen exposure less than the upper 95 percent CI for the cumulative ED<sub>05</sub> of all allergens investigated (Turner *et al.*, 2022). In fact, consistent with data suggesting that soybean is an uncommon cause of anaphylaxis globally (Baseggio Conrado, Turner and Patel, 2021), no cases of anaphylaxis to low (< 200 mg protein) levels of exposure were identified (Turner *et al.*, 2022).

### **Recommendation**

The lower of the discrete or cumulative ED<sub>05</sub> estimates for soy was 10.0 mg total protein. If the ED<sub>05</sub> was rounded strictly in accordance with the principles followed in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b), no further rounding would be necessary, leading to an RfD for soy of 10 mg total protein from soy.

## A1.4 CELERY/CELERIAC

Celery/celeriac is a priority allergen in one Codex region, with geographic distribution of reported allergic reactions largely limited to a few countries in Europe.

### Available and accessible studies

As detailed in the supplementary information from Remington *et al.* (2020), there are four studies available for celery/celeriac (four from published literature) with a total of 82 individuals included in the analysis (14 left-censored, 18 right-censored); 66 identified as adults, and four identified as children.

### Quality and quantity

In Part 1 of this Ad hoc Joint FAO/WHO Expert Consultation, analysis of the potency data from Remington *et al.* (2020) and Houben *et al.* (2020) showed an adequate quantity of data available for dose-distribution modelling (n = 82) and a high potential for biases in the available data for celery/celeriac. The amount of available potency data for celery/celeriac was similar to that for fish (n = 82 data points), shrimp (n = 75 data points), soy (n = 82 data points), walnut (n = 74 data points) and wheat (n = 99 data points).

The high potential for biases with the available data for celery/celeriac was attributed because available data were mostly from central Europe (Switzerland, Germany, Italy, France and Poland; one from the Kingdom of the Netherlands), and more than a third of the data were right- or left-censored (FAO and WHO, 2022a).

The ED<sub>05</sub> of the discrete dosing scheme was established at 1.5 mg protein (CI 95 percent: 0.3, 11.8) with the Bayesian stacked model averaging methodology, and the ED<sub>05</sub> of the cumulative dosing scheme was established at 1.3 mg protein (CI 95 percent: 0.2, 7.9) for celery/celeriac (Remington *et al.*, 2020). Relatively large confidence intervals for both ED<sub>05</sub>s can be partially attributed to the high proportion of right-censored data. There is no single-dose challenge study available to verify the ED<sub>05</sub> for celery/celeriac in an unselected outpatient clinic population. All data are derived from studies using celery tuber (celeriac) (*Apium graveolens* var. *rapaceum*) (or extracts thereof). No data have been generated with celery stalk or celery seed (*Apium graveolens* var. *graveolens*). The Expert Committee noted that celery/celeriac was frequently used in forms where it was a hidden ingredient (e.g. as a spice).

Celery/celeriac was determined to belong to the second lowest grouping for severity (Group C [II] – Level 1 evidence - Higher proportion of anaphylaxis, one region) (FAO and WHO, 2022a).

### Recommendation

The lower of the discrete or cumulative ED<sub>05</sub> estimates for celery/celeriac was 1.3 mg total protein from celery/celeriac. Rounding the ED<sub>05</sub> strictly in accordance with the principles followed in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b) leads to an RfD for celery/celeriac of 1 mg total protein from celery/celeriac.

## A1.5 LUPIN

### Available and accessible studies

As detailed in the supplementary information from Remington *et al.* (2020), there are four studies available for lupin (three from published literature) with a total of 25 individuals included in the analysis (one left-censored, nine right-censored), 16 identified as adults.

### Quality and quantity

In Part 1 of this Ad hoc Joint FAO/WHO Expert Consultation, analysis of the potency data from Remington *et al.* (2020) and Houben *et al.* (2020) showed a poor quantity of data available for dose-distribution modelling (n = 25) and a high potential for biases with the available data for lupin. The amount of available potency data for lupin was similar to that for mustard (n = 33 data points) and buckwheat (n = 26 data points).

The high potential for biases in the available data for lupin was attributed to available data being only from Europe (Italy, France, the United Kingdom of Great Britain and Northern Ireland and the Kingdom of the Netherlands) with more than a third of the data being right- or left-censored (FAO and WHO, 2022a).

The ED<sub>05</sub> of the discrete dosing scheme was established at 15.3 mg protein (CI 95 percent: 6.7, 47.0) with the Bayesian stacked model averaging methodology, and the ED<sub>05</sub> of the cumulative dosing scheme was established at 16.8 mg protein (CI 95 percent: 4.7, 70.0) (Remington *et al.*, 2020). Relatively large confidence intervals for both ED<sub>05</sub>s can be partially attributed to the high proportion of right-censored data. There is no single-dose challenge study available to verify the ED<sub>05</sub> for lupin in an unselected outpatient clinic population.

Lupin was determined to belong to the second highest grouping for severity (Group B – Level 2 evidence – Higher proportion of anaphylaxis in 1–2 CODEX regions) (FAO and WHO, 2022a). Lupin belongs to the Fabaceae (Leguminosae), which encompasses many edible plants, including soy and peanut.

In discussion, the Expert Committee questioned whether a valid RfD could be set for lupin given the low quantity and quality of the data for dose-distribution modelling. They also observed that as a result it is scientifically not possible to set an RfD for lupin from a *risk assessment* perspective. At the same time, they agreed that on a precautionary basis, a value of 10 mg aligning with that of soy could be set from a *risk management* perspective. However, while they agreed that setting a value was helpful in relation to allergen management and public health, the recommendation should stress the limitations of the data and could be changed if and when adequate data emerge.

## Recommendation

The lower of the discrete or cumulative ED<sub>05</sub> estimates for lupin was 15.3 mg total protein from lupin. If the ED<sub>05</sub> was rounded strictly in accordance with the principles followed in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens (FAO and WHO, 2022b), the value for risk management for lupin would be 15 mg total protein from lupin. However, a more conservative rounding reflecting the greater uncertainty about the true value and taking into account the phylogenetic relationship leads to a recommended value for risk management of 10 mg total protein from lupin. The Expert Committee underlined that the value for lupin is not based on a risk assessment but should be considered a value for risk management purposes and therefore subject to change if and when better quantity or quality of data emerge.

## A1.6 MUSTARD

### Available and accessible studies

As detailed in the supplementary information from Remington *et al.* (2020), there are three studies available for mustard (three from published literature) with a total of 33 individuals included in the analysis (two left-censored, ten right-censored); nine identified as adults, and 24 identified as children.

### Quality and quantity

In Part 1 of this Ad hoc Joint FAO/WHO Expert Consultation, analysis of the potency data from Remington *et al.* (2020) and Houben *et al.* (2020) showed a poor quantity of data available for dose-distribution modelling ( $n = 33$ ) and a high potential for biases in the available data for mustard. The amount of available potency data for mustard was similar to that for lupin ( $n = 25$  data points) and buckwheat ( $n = 26$  data points).

The high potential for biases in the available data for mustard was attributed to available data being only from two countries in Europe (Spain and France) with more than a third of the data being right- or left-censored (FAO and WHO, 2022a).

The ED<sub>05</sub> of the discrete dosing scheme was established at 0.4 mg protein (CI 95 percent: 0.1, 3.6) with the Bayesian stacked model averaging methodology, and the ED<sub>05</sub> of the cumulative dosing scheme was established at 0.5 mg protein (CI 95 percent: 0.09, 3.9) (Remington *et al.*, 2020). Relatively large confidence intervals for both ED<sub>05</sub>s can be partially attributed to the high proportion of right-censored data.

In Report 1, mustard was the only food to be designated “high” in the potency criteria, but the report made a special comment regarding the ED values for mustard and stated:

However, it should be noted that the 95 percent confidence intervals for one or both the mustard ED<sub>10</sub> and ED<sub>50</sub> estimates overlap with the 95 percent confidence intervals for cashew, celery, egg, hazelnut, lupin, milk, peanut, sesame, walnut and wheat. Thus, while the potency decision is labelled as “high” for mustard, there is a large level of overlap of ED<sub>p</sub> estimates between mustard and the foods designated “medium” potency (FAO and WHO, 2022a, p.42).

Similar overlap can be observed at the ED<sub>01</sub> and ED<sub>05</sub> levels (Remington *et al.*, 2020).

There is no single-dose challenge study available to verify the ED<sub>05</sub> for mustard in an unselected outpatient clinic population. Mustard was determined to belong to the second lowest grouping for severity (Group C [II] – Level 2 evidence – Higher proportion of anaphylaxis, one region) (FAO and WHO, 2022a).

In discussion, the Expert Committee questioned whether a valid RfD could be set for mustard given the low quality and quantity of the data for dose-distribution modelling. It concluded that it is scientifically not possible to set an RfD for

mustard from a *risk assessment* perspective. However, the committee agreed that on a precautionary basis, a value of 1 mg aligning with other foods designated as “medium” potency could be set from a *risk management* perspective. The value of 1 mg was preferred to the ED<sub>05</sub> values derived from dose-distribution modelling of mustard because of the bias introduced by the high proportion of right-censored observations (10 out of 30). However, while the Expert Committee agreed that setting a value was helpful in relation to allergen risk management and public health, the recommendation should stress the limitations of the data which could therefore be subject to change if and when more adequate data emerge.

### **Recommendation options**

While a discrete ED<sub>05</sub> was estimated at 0.4 mg total protein from mustard and a cumulative ED<sub>05</sub> of 0.5 mg, the values were heavily influenced by the number of right-censored observations. The confidence intervals for those ED<sub>05</sub> values overlapped considerably with those for many allergenic foods of similar (medium) potency. A value of 1 mg aligning with the lowest RfD for “medium potency” foods is recommended from a *risk management* perspective. This also aligns with the 1 mg RfD for most higher potency tree nuts. The Expert Committee underlined that the value for risk management for mustard is not based on a risk assessment but should be considered a value for risk management purposes and therefore subject to change if and when better quantity or quality of data emerge.



## A1.7 BUCKWHEAT

### Available and accessible studies

Buckwheat is a regulated food allergen in Japan and the Republic of Korea. As detailed in the supplementary information from Remington *et al.* (2020), there are two studies available for buckwheat (one from published literature) with a total of 26 individuals included in the analysis (zero left- censored, one right-censored); 24 identified as adults in the published study, and two identified as children.

### Quality and quantity

In Part 1 of this Ad hoc Joint FAO/WHO Expert Consultation, analysis of the potency data for buckwheat was not completed due to the lack of available dose-distributions (FAO and WHO, 2022a). However, analysis of the potency data available shows a poor quantity of data available for dose-distribution modelling ( $n = 26$ ) and a high potential for biases with the available data for buckwheat (Remington *et al.*, 2020). The amount of available potency data for buckwheat was similar to that for mustard ( $n = 33$  data points) and lupin ( $n = 25$  data points).

The high potential for biases with the available data for buckwheat was attributed to 24 of the 26 subjects being part of a single study in Italy (Heffler *et al.*, 2011) and was due to the lack of data in the clinical range of interest (below the ED<sub>15</sub> on the Kaplan-Meier curves). The three most sensitive individuals tolerated a dose of 9 mg buckwheat protein and reacted to 54 mg buckwheat protein, which limits the data available in the range of interest for dose-distribution modelling (below the ED<sub>15</sub> on the Kaplan-Meier curves). As such, the distribution for buckwheat was not extrapolated outside of the data range, and the buckwheat dataset was deemed insufficient for ED<sub>01</sub> or ED<sub>05</sub> derivation (Remington *et al.*, 2020).

However, looking at predicted ED<sub>05</sub> values below the experimental data range, experts noted that the ED<sub>05</sub> of the discrete dosing scheme was estimated at 35.9 mg protein (CI 95 percent: 11.3, 150) with the Bayesian stacked model averaging methodology, and the ED<sub>05</sub> of the cumulative dosing scheme was estimated at 54.1 mg protein (CI 95 percent: 15.1, 252) (unpublished analysis provided by Professor Houben, TNO, the Kingdom of the Netherlands, see Annex 3). Relatively large confidence intervals for both ED<sub>05</sub>s can be partially attributed to a single study or a single-dosing scheme heavily influencing the results. There is no single-dose challenge study available to verify the ED<sub>05</sub> for buckwheat in an unselected outpatient clinic population.

Buckwheat was determined to belong to the second lowest grouping for severity (Group C [II] – Level 1 evidence - Higher proportion of anaphylaxis, one region) (FAO and WHO, 2022a).

In discussion, the Expert Committee questioned whether a valid RfD could be set for buckwheat given the low quality and quantity of the data for dose-distribution modelling.

The committee concluded that it is scientifically not possible to set an RfD for buckwheat from a *risk assessment* perspective. However, it agreed that on a precautionary basis, it would be helpful to set a value from a *risk management* perspective. The value of 10 mg was preferred to the ED<sub>05</sub> values derived from dose-distribution modelling of buckwheat because of the small number of data points and the observation that they did not encompass values the ED<sub>15</sub>. However, while the Expert Committee agreed that setting a value was helpful in relation to allergen risk management and public health, the recommendation should stress the limitations of the data and emphasize that it could be changed if and when adequate data emerge.

### **Recommendation**

Buckwheat is from the Caryophyllales order and the Polygonaceae family (Allergen Nomenclature, 2023a, b). None of the other allergenic foods on the global priority allergen list or on the list of foods discussed as potential allergens of national or regional interest belong to the Caryophyllales order (FAO and WHO, 2022a; Allergen Nomenclature, 2023c). There is no taxonomic argument for comparison or grouping purposes. However, potency data suggest that buckwheat is closer to that of soy than to other priority allergenic foods, with reactions to 54 mg buckwheat protein, but not 9 mg. On that basis a value of 10 mg, aligning with the soy RfD, is recommended from a *risk management* perspective. The Expert Committee underlined that the value for buckwheat is not based on a risk assessment but should be considered a value for risk management purposes and therefore subject to change if and when better quantity or quality of data emerge.

## A1.8 OATS

In Report 1, the Expert Committee in its consideration of the list of global priority allergens discussed oats as well as other cereals listed in the category “cereals containing gluten” and made the following observations (FAO and WHO, 2022a):

The evidence that rye, barley and oats cause IgE-mediated allergies is weak (p. 94).

IgE cross-reactivity between wheat, barley and rye proteins may also extend to include oats (Varjonen *et al.*, 1994). However, a recent study of severe wheat allergy suggested that evidence of cross-reactivity with oats was weak (Srisuwatchari *et al.*, 2020). There is evidence of sensitization to oats occurring as a consequence of using topical creams based on oats (Boussault *et al.*, 2007) although this was not confirmed in a later study (Goujon *et al.*, 2009). There are few if any case reports of IgE-mediated allergies to oats due to ingestion, although traces of wheat, rye and barley may cause reactions in susceptible individuals (p. 78).

Oats are not considered to be a priority allergenic food because they pose a low public health risk of causing IgE-mediated allergy and [coeliac toxicity] (p. 67).<sup>2</sup>

It might be considered that oats should be on a regional priority allergen list because oats are generally contaminated, and often at significant levels, with gluten-containing cereals (p. 67).

On the basis of those observations, the Expert Committee concluded that oats did not meet the criteria to be a global priority allergen but could be included on regional lists of priority allergens (FAO and WHO, 2022a). The underlying reasoning behind this conclusion was that data on oats were extremely limited or missing in the three categories of data used for prioritization:

- > No estimate of prevalence of IgE-mediated allergy to oats could be established, with a very limited number of case reports as the only evidence.
- > No estimate of severity could be established through scrutiny of anaphylaxis registry data, as used for other allergenic foods.
- > No data could be identified for dose-distribution modelling. Double-blind, placebo-controlled food challenge (DBPCFC) studies in individuals with oat allergy are rare. There is no publicly available evidence that the low mg protein amounts of concern for most of the other priority allergenic foods are also a concern for individuals with IgE-mediated allergy to oats.

In its discussion of the CCFL request regarding establishment of RfDs for regional or national allergens that did not meet the criteria to be global priority allergens,

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<sup>2</sup> Text within brackets [] contains an editorial change from the original quote for clarity.

the Expert Committee identified two concerns behind the inclusion of oats in the request:

- > unintended presence of gluten through cross-contact between oats and other cereals containing gluten, leading to a risk of IgE-mediated reactions and exacerbation of coeliac disease through consumption of oats; and
- > induction or exacerbation of coeliac disease in the subpopulation of people with coeliac disease who report having symptoms on exposure to “gluten-free” oats.

The Expert Committee noted these concerns and concluded that they would not be addressed by recommending an RfD or even a management value for oats as the data were lacking to support such an approach. The Expert Committee suggested that the issue of cross-contact with gluten-containing cereals would be best addressed through general allergen risk management processes. The Expert Committee also noted that as for all other foods, cross-contamination of oats by other grains must be managed in ways that control the production, processing, transport and handling of oats. Management of this issue should not misuse a valuable risk management tool, such as through the generic labelling of all oat products as allergens, on the basis of the possible accidental inclusion of varying amounts of cereals containing gluten.

### Recommendation

Reference doses have been developed for the management of IgE-mediated allergies. While IgE-mediated reactions to oats have been reported, available data indicate that they are extremely rare and the consequent lack of data of any of the types required precludes the setting of an RfD for oats. In other words, there is no basis for an oat specific RfD, and it would not be appropriate to recommend one.

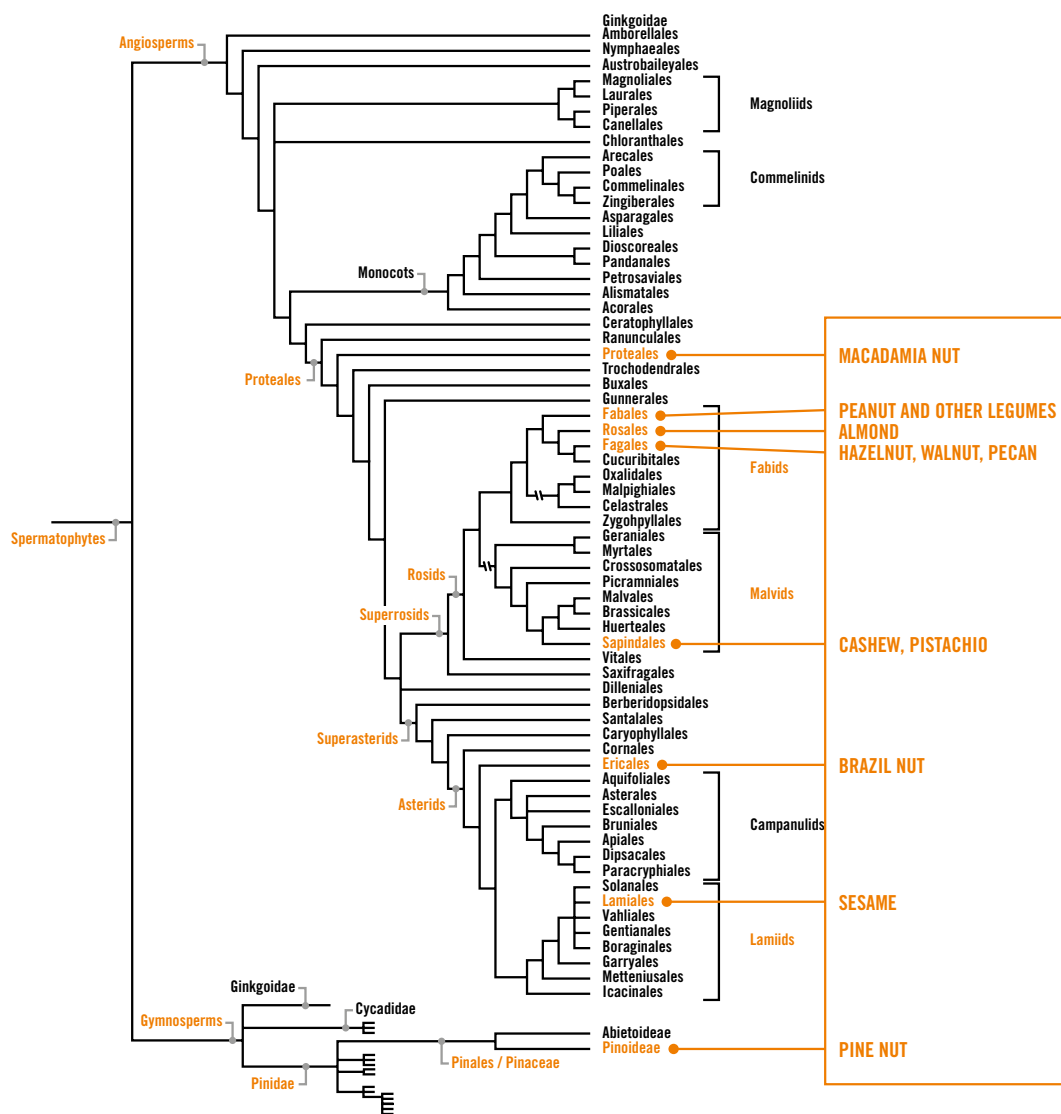
A major concern underlying the use of oats is contamination with wheat and related cereals, barley or rye, resulting in concentrations of gluten potentially significant in the context of IgE-mediated reactions or exacerbation of coeliac disease. The Expert Committee expressed the view that this issue should be handled through general allergen risk management processes.

The Expert Committee recognized the concern about coeliac disease manifestations triggered by consumption of oats in a small proportion of people with coeliac disease. However, they noted that most studies support the safety of oats for people with coeliac disease (Pinto-Sánchez *et al.*, 2017) and the issue of oats as a causative or exacerbating factor in coeliac disease is a field where further research is needed (Ciacci *et al.*, 2015). Recommending an RfD, particularly one based on an IgE-mediated allergy to oats, would not address the issue.

# ANNEX 2

Figure A1 represents the families of specific tree nuts and other selected allergenic foods that have been indicated on the phylogenetic tree. Due to the inclusion of pine nut, the angiosperm classification of orders and families from the Angiosperm Phylogeny Group *et al.* (2016) was adapted to include both angiosperms and a simplified gymnosperms representation in the spermatophytes (seed plants) branch.

FIGURE A1. **FAMILIES OF SPECIFIC TREE NUTS AND OTHER SELECTED ALLERGENIC FOODS ON THE PHYLOGENETIC TREE**



Source: **The Angiosperm Phylogeny Group et al.** 2016. An update of the Angiosperm Phylogeny Group classification for the orders and families of flowering plants: APG IV. *Botanical Journal of the Linnean Society*, 181(1): 1–20. <https://doi.org/10.1111/boj.12385>

# ANNEX 3

Details regarding buckwheat data and model averaging eliciting dose-distributions (unpublished data generated and provided by Professor Houben, TNO, the Kingdom of the Netherlands; data derived from the TNO FARRP Threshold Database; for details regarding the database, data inclusion criteria and the methodology, see Remington *et al.* 2020 and Houben *et al.* 2020).

Available data on buckwheat:

TABLE A1 STUDIES REPORTING FOOD CHALLENGES TO BUCKWHEAT

STUDY	COUNTRY	NUMBER TESTED		FIRST DOSE (MG PROTEIN)	TOTAL NO WITH OBJECTIVE SYMPTOMS	RIGHT CENSORED	LEFT CENSORED
		ADULTS	CHILDREN				
HEFFLER <i>ET AL.</i> (2011)	ITALY	24	0	9	24	0	0
UNIVERSITY MEDICAL CENTER GRONIGEN (UMCG) (UNPUBLISHED)	NETHERLANDS (KINGDOM OF THE)	0	2	18	2	1	0

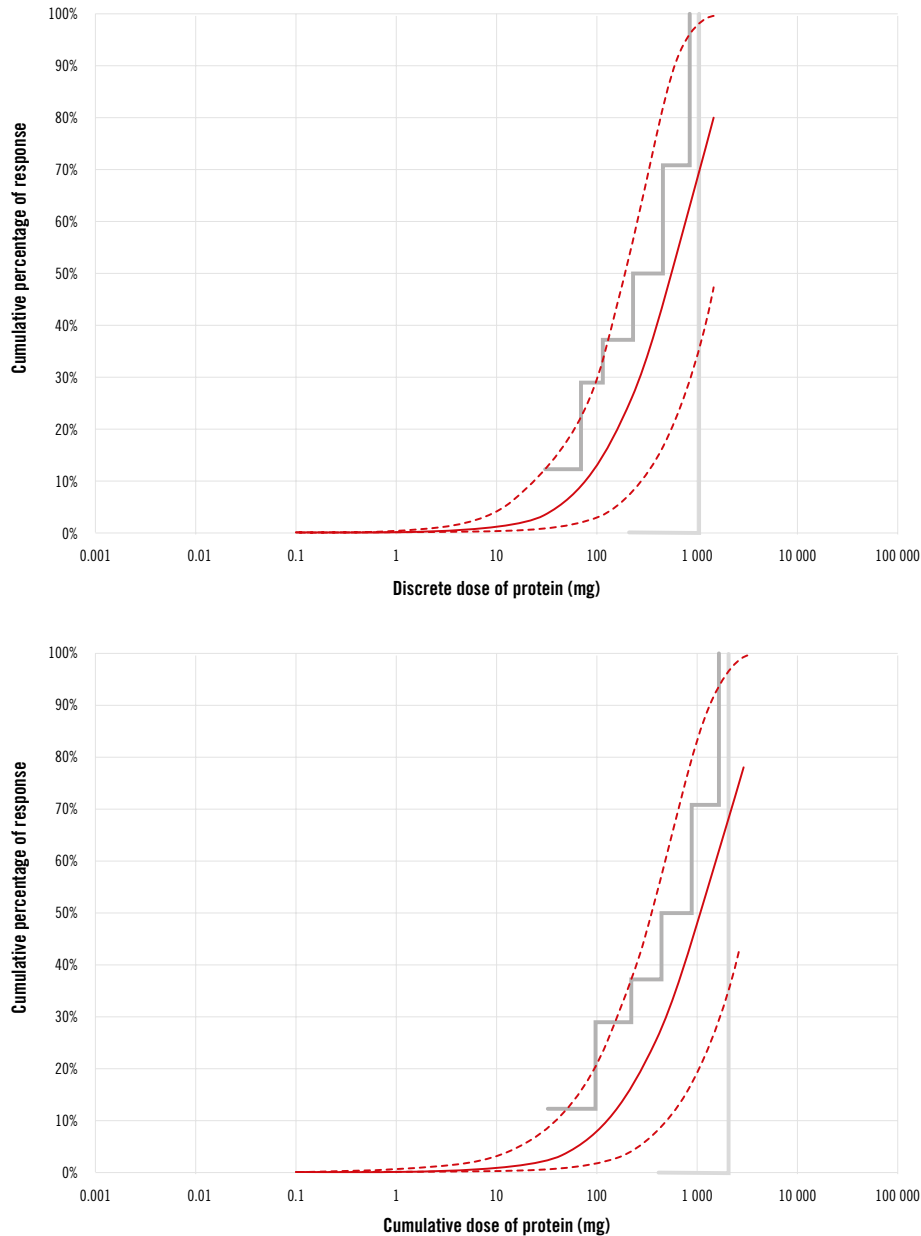
Source: Heffler, E., Nebiolo, F., Asero, R., Guida, G., Badiu, I., Pizzimenti, S., Marchese, C. *et al.* 2011. Clinical manifestations, co-sensitizations, and immunoblotting profiles of buckwheat-allergic patients: Buckwheat allergy in a series of 24 patients. *Allergy*, 66(2): 264–270. <https://doi.org/10.1111/j.1398-9995.2010.02469.x>; UMCG (unpublished).

The three most sensitive individuals tolerated a dose of 9 mg buckwheat protein and reacted to 54 mg buckwheat protein, which limits the data available in the range of interest for dose-distribution modelling (below the ED<sub>15</sub>). It should be noted that in prior publications the distribution for buckwheat was not extrapolated outside of the data range and the buckwheat dataset was deemed insufficient for ED<sub>01</sub> or ED<sub>05</sub> derivation (Remington *et al.*, 2020).

However, if looking at predicted ED<sub>05</sub> values (below the experimental data range), experts note that the ED<sub>05</sub> of the discrete dosing scheme was estimated at 35.9 mg protein (CI 95 percent: 11.3, 150) with the Bayesian stacked model averaging methodology and that the ED<sub>05</sub> of the cumulative dosing scheme was estimated at 54.1 mg protein (CI 95 percent: 15.1, 252).

Model average threshold distribution curves based on the discrete (left) and cumulative (right) dose of total buckwheat protein:

**FIGURE A2. DOSE DISTRIBUTION MODELLING UTILIZING BAYESIAN STACKED MODEL AVERAGING METHODOLOGY FOR BUCKWHEAT, BASED ON DISCRETE (UPPER GRAPH) AND CUMULATIVE (LOWER GRAPH) DOSE DATASETS. DOSES ARE EXPRESSED MG BUCKWHEAT PROTEIN. THE PREDICTED DOSE 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 (GREY LINES, DARKER INDICATES STUDY WITH MORE OBSERVATIONS).**



Source: Unpublished data generated and provided by Houben, TNO, the Kingdom of the Netherlands.

Corresponding model average eliciting doses (EDs):

TABLE A2 **ED<sub>01</sub> TO ED<sub>10</sub> VALUES FROM THE MODEL AVERAGED POPULATION THRESHOLD DOSE DISTRIBUTIONS FOR BUCKWHEAT, BASED ON DISCRETE AND CUMULATIVE DOSE DATASETS. ED VALUES ARE EXPRESSED IN MG TOTAL BUCKWHEAT PROTEIN. THE 95% CONFIDENCE INTERVAL IS REPRESENTED BY THE LOWER CONFIDENCE INTERVAL (LCI) AND THE UPPER CONFIDENCE INTERVAL (UCI).**

ED	DISCRETE			CUMULATIVE		
	BUCKWHEAT	BUCKWHEAT LCI	BUCKWHEAT UCI	BUCKWHEAT	BUCKWHEAT LCI	BUCKWHEAT AT UCI
ED <sub>01.0</sub>	6.6	1.7	40	8.2	1.8	58.3
ED <sub>02.0</sub>	13.7	3.9	69.8	18.5	4.6	108
ED <sub>03.0</sub>	21	6.2	97.5	29.8	7.8	157
ED <sub>04.0</sub>	28.4	8.7	124	41.7	11.3	204
ED <sub>05.0</sub>	35.9	11.3	150	54.1	15.1	252
ED <sub>06.0</sub>	43.5	14	175	67.1	19.2	300
ED <sub>07.0</sub>	51.3	16.7	200	80.4	23.5	348
ED <sub>08.0</sub>	59.1	19.6	225	94.2	28	396
ED <sub>09.0</sub>	67	22.4	250	108	32.6	445
ED <sub>10.0</sub>	75	25.4	275	123	37.4	495



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# RISK ASSESSMENT OF FOOD ALLERGENS

## PART 5: REVIEW AND ESTABLISH THRESHOLD LEVELS FOR SPECIFIC TREE NUTS (BRAZIL NUT, MACADAMIA NUT OR QUEENSLAND NUT, PINE NUT), SOY, CELERY, LUPIN, MUSTARD, BUCKWHEAT, AND OATS

### MEETING REPORT

In Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens, reference doses (RfDs) were recommended for the global priority allergens, which included: walnut (and pecan), cashew (and pistachio), almond, peanut, egg, hazelnut, wheat, fish, shrimp, milk and sesame. Still, RfDs were not recommended for a number of regional or national priority allergens as they did not meet the criteria to be global priority allergens.

In an additional request, the Codex Committee on Food Labelling (CCFL) indicated interest in potential RfD derivation for the following specific food allergens: specific tree nuts (Brazil nut, macadamia nut or Queensland nut, pine nut), soy, celery, lupin, mustard, buckwheat, and oats.

An overview of the available data and recommended RfDs (or reasons no RfD could be derived) are given here for these specific food allergens. These RfDs were derived following the guidelines described in Part 2 of the Ad hoc Joint FAO/WHO Expert Consultation for deriving an RfD for priority allergenic foods. Details of the available data and discussions of the Expert Committee are presented in this report.

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