Food and Agriculture Organization of the United Nations

World Health Organization

Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens
Part 2: Review and establish threshold levels in foods of the priority allergens

Virtual meeting, 15 March – 2 April 2021

SUMMARY AND CONCLUSIONS

Issued on 20 August 2021

The second in a series of three meetings of an ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens was held from 15 March to 2 April 2021. The main purpose of this second meeting was to establish threshold levels in foods of the priority allergens[1].

If conditions had permitted, this meeting would have been held at FAO headquarters in Rome, Italy. Because of the travel restrictions and lock-downs due to the COVID-19 pandemic in many countries, the joint FAO/WHO secretariat was unable to convene a physical meeting. Therefore, the meeting was held as a videoconference using a virtual online platform.

In view of the time differences in the countries of origin of the invited experts, the time for a videoconference was restricted to a 3-hour time slot (12:00–15:00 CET) each day. To make up for the usual daily length (8–10 hours) of a joint FAO/WHO scientific expert meeting and efficiencies associated with in-person meetings, virtual sessions were held daily over the course of three weeks.

Dr René Crevel served as Chairperson.

Dr Benjamin Remington served as rapporteur.

An Expert Committee, comprising scientists, regulators, physicians, clinicians and risk managers from academia, government and the food industry were selected to participate in the second meeting of the FAO/WHO Expert Consultation on Risk assessment of Food Allergens.

Establishing thresholds constitutes a critical first step to assessing the risk from allergens, as they are a characteristic of the hazard that allergens present to the food-allergic population. Their establishment is thus essential to evidence-based application of risk management and mitigation strategies, such as Precautionary Allergen Labelling (PAL), which are a focus of the Terms of Reference (ToR)[2] for the third meeting. The Expert Committee followed the ToR as formulated, except that they considered the list of

[1] http://www.fao.org/3/cb4653en/cb4653en.pdf
[2] http://www.fao.org/3/ca7121en/ca7121en.pdf

priority allergens decided at the first meeting of this FAO/WHO Consultation. The ToR clearly signaled that the Codex Committees looked to define threshold levels that were Health-Based Guidance Values (HBGV). Guided by the definition of HBGV in Environmental Health Criteria (EHC) 240 Chapter 5[3], The Expert Committee considered and deliberated the following four approaches to identify which one(s) is/are best suited to define threshold levels for food allergens:

- Analytical-based,
- No Observed Adverse Effect Level [NOAEL] + Uncertainty Factor [UF],
- Benchmark Dose combined or not with the application of a Margin of Exposure, and
- Probabilistic Hazard Assessment.

Following discussions for each approach, the Expert Committee concurred that the principle of establishing a Benchmark Dose (without the application of a Margin of Exposure) and the Probabilistic Hazard Assessment approach most closely aligned with the charge.

This document summarizes the conclusions of this meeting and is made available to facilitate the deliberations of the upcoming Codex Committee on Food Labelling (CCFL) and Codex Committee on Food Hygiene (CCFH). The full report of the meeting will be published as part of the Food Safety and Quality Series and will describe the scientific evidence available to the Expert Committee and its deliberations during the meeting.

The meeting participants are listed in Annex 1 of this summary report.

More information on this work is available at:

http://www.fao.org/food-safety/en/

and

https://www.who.int/foodsafety/en/

[3] https://www.who.int/publications/i/item/9789241572408

Background and objective

At its 45th session in May 2019, the CCFL requested FAO and WHO to provide scientific advice to validate, and if necessary, update the list of foods and ingredients in section 4.2.1.4 of GSLPF (General standard for the labelling of prepackaged foods) (FAO and WHO, 2019). This request was addressed at the first meeting of the *Ad hoc* Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens by first establishing the criteria for assessing additions and exclusions to the priority food allergen list, then evaluating the available evidence for foods of concern. The establishment of "thresholds below which the majority of allergic consumers would not suffer an adverse reaction" for the priority allergens identified at the first meeting forms part of the Codex requests.

In response to the requests from the CCFH (FAO and WHO, 2018), the objectives of the expert consultation were:

- What are the threshold levels for the priority allergens below which the majority of allergic consumers would not suffer an adverse reaction?
- For the priority allergens, what are appropriate analytical methods for testing food and surfaces?
- What should be the minimum performance criteria for these different analytical methods?

Thus, FAO and WHO re-convened the *Ad hoc* Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens for a second meeting to provide scientific advice on this subject (Annex 2).

Conclusions

Based on the defined approach, the Expert Committee discussed and agreed on the safety objective, which could be described as "*to minimise, to a point where further refinement does not meaningfully reduce health impact, the probability of any clinically relevant objective allergic response, as defined by dose distribution modelling of minimum eliciting doses (MEDs) and supported by data regarding severity of symptoms in the likely range of envisioned Reference Doses (RfD)*". The Committee further identified several important considerations to guide decision-making. These included a clear definition of criteria to be met by quantitative data on which reference doses (RfD) are based, supporting data on health manifestations (severity) at the proposed RfD, quality, quantity, availability and accessibility of data (for priority allergens), as well as how to deal with priority allergens for which information supporting one or more of those considerations was lacking.

The Expert Committee then considered the form of the outputs, starting from eliciting dose (ED) values predicted to result in objective reactions in no more than 1% (ED01) and 5% (ED05) of the allergic population for the priority allergens. These ED values have already been shown to be protective in single dose challenge studies for peanut and milk, but also through general experience with VITAL 2.0/3.0, and evaluations by expert committees such as Belgium's Scientific Committee Of The Federal Agency For The Safety Of The Food Chain (FASFC).They agreed as a general principle that the RfD values should be contextualised, taking into account the wider and unintended consequences. Importantly, they concluded that a guiding principle should be whether selecting a more stringent (lower) ED value would materially improve the public health impact.

As data availability and quality are critical to the sound derivation of EDp[4] values, the Expert Committee discussed potential data sources. They noted that the data reported in the publications of Remington, *et al*., (2020) and Houben, *et al*., (2020) were the most comprehensive and best described source available, both in terms of content and curation, with supportive peer-reviewed publications. Dose-distribution analysis methodology was similarly well-described within this dataset. The Committee reviewed the data sources for each priority allergen, taking into consideration both included publications and those which had been collated but excluded, and the extent and type of bias in the data.

Characterising the hazard forms a critical component of risk assessment and considers both the numbers of people with the relevant allergy who will be affected by exposure to any given amount of allergen and the characteristics of any reaction that may occur. The first element is covered by dose-distribution modelling, which is now well understood and developed. The second element is an evaluation of the likely health impact. A key factor that impacts the health of allergic individuals is reaction severity. Severity is a complex and multidimensional concept with an ill-defined relationship to dose; as such severity data suitable for modelling are limited. Two principal sources of data were reviewed: 1) evidence of anaphylactic reactions in clinical data at defined doses and 2) data on symptoms associated with reactions up to and including the ED01, ED05 and ED10 reported by Remington, *et al*. (2020) and Houben, *et al*. (2020). The latter indicated that all symptoms up to ED05 fell into a mild or moderate category, while analysis of clinical data indicated that up to 5% of reactions at both ED01 and ED05 could be classed as anaphylaxis, although none were severe, based on the World Allergy Organisation definition. Furthermore, the Committee noted the extreme rarity of fatal food anaphylaxis (1 per 100000 person-years in the allergic population) and observed that no fatal reactions had been observed following exposure to doses at or below those considered for RfD (i.e. the ED01 and the ED05). Considering both the proportion of individuals potentially affected and the severity characteristics of reactions at ED01 and ED05, including the absence of reports of severe anaphylaxis, the Committee agreed that, for all priority allergens, the safety objective would be met by starting the definition of RfD at the ED05 (as evaluated using the data from Remington, *et al*. (2020) and Houben, *et al*. (2020)). To make the application simpler, the Committee further simplified its recommendations by rounding the ED05 values down to one significant figure (with some exceptions for allergens with limited data). Those foods with close ED05 values were then grouped together and a single value derived for the RfD, further rounding down the value, if necessary. The resulting RfDs as mg of protein from the allergenic source are summarised in the table below.

[4]"EDp" designates a population threshold, where "p" defines the proportion (%) predicted to react at that threshold (dose).

	RfD Recommendation (mg total protein from the allergenic source)
Walnut (and Pecan*)	**1.0**
Cashew (and Pistachio*)	**1.0**
Almond**	**1.0**
Peanut	**2.0**
Egg	**2.0**
Hazelnut	**3.0**
Wheat	**5.0**
Fish	**5.0**
Shrimp	**200**
Milk	**[decision pending based on further data analysis]**
Sesame	**[decision pending based on further data analysis]**
*** see considerations in full report ** provisional**	

The Committee further incorporated into their recommendations action levels, using approaches applied for other food hazards. The action levels were calculated for different intakes of the affected food (containing potential unintended allergen), ranging from 10g to 510g in 10g increments.

Examining assay capability in relation to the recommended RfD, the Committee observed that RfD can be implemented and monitored to some degree with current analytical capabilities but acknowledged that significant limitations in method performance exist. They strongly recommended that expression of analytical results be standardized as mg total protein of the allergenic food per kg food product analysed, in order to facilitate result interpretation and comparison with a RfD and action level by users of analytical services. To address deficiencies in analytical methodology, they recommended the development of method performance criteria, as well as more extensive provision of accessible reference materials for the priority allergens. Experts 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 ELISA, which are critical to assay performance. Improvements were also called for in sampling for analysis and curation of samples from originator to laboratory.

References

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Annex 1. List of participants

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Annex 2. Meeting plan of the Ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens

Meeting 1: Review and validation of Codex priority allergen list through risk assessment (November – December 2020)

I. Whether the published criteria for assessing additions and exclusions to the list is still current and appropriate.
II. Subject to the advice on the criteria above:
    - Whether there are foods and ingredients that should be added to or deleted from the list.
    - Clarification of the groupings of foods and ingredients in the list.
    - Whether certain foods and ingredients, such as highly refined foods and ingredients, that are derived from the list of foods known to cause hypersensitivity can be exempted from mandatory declaration.

Meeting 2: Review and establish threshold levels in foods of the priority allergens (March – April 2021)

I. What are the threshold levels for the priority allergens below which the majority of allergic consumers would not suffer an adverse reaction?
II. For the priority allergens, what are appropriate analytical methods for testing food and surfaces?
III. What should be the minimum performance criteria for these different analytical methods?

Meeting 3: Review and evaluate the evidence in support of precautionary labelling (October 2021)

I. What methods/tools are available for FBOs to determine:
    - whether allergen cross-contact is reasonably likely to occur in a food after a cleaning procedure;
    - whether allergen cross-contact is reasonably likely to occur from equipment used for foods with different allergen profiles; and
    - the level of allergen in a food resulting from cross-contact?
II. Guidance on precautionary labelling.
    - The use of scientifically based threshold levels to evaluate risk for consumers with food allergies.
    - Determine the conditions for using the precautionary allergen labelling.
III. How can thresholds be used by FBOs to determine:
    - the extent to which a cleaning procedure removes an allergen to a level that prevents or minimises the risk to the majority of allergic consumers from allergen cross-contact; and
    - whether an ingredient that contains a low level of an allergen (e.g. an ingredient with a precautionary allergen label) warrants control of its use to prevent or minimise allergen cross-contact?