TOX/2023/35: Annex A

Committee on the Toxicity of Chemicals in Food, Consumer Products and the Environment.

Draft assessment of the Codex report on food allergen thresholds

Background

1. At the 45th session of the Codex Committee on Food Labelling (CCFL) held in May 2019, the FAO and WHO were asked to provide scientific advice on the following subjects by establishing an ad hoc Joint FAO/WHO Expert Consultation on Risk Assessment of Food Allergens:

- Validation of Codex's priority allergen list through risk assessment.
- Threshold levels in foods of the priority allergens.
- Appropriate use of precautionary allergen labelling (PAL).
- Review and establish exemptions for the food allergens.

2. The summary and conclusions report on threshold levels was published in August 2021, and the full report was published in January 2023: Risk assessment of food allergens. Part 2: review and establish threshold levels in foods for the priority allergens: meeting report. The full report recommended reference doses (RfD) as mg of protein for certain allergens based on ED_{05} values (Houben et al, 2020; Remington et al, 2020). ED_{05} is the eliciting dose predicted to provoke reactions in 5% of the allergic population.

3. Food allergen risk assessments produced by the Food Standards Agency (FSA) and some members of the food industry are conservative and therefore based on the use of ED_{01} (i.e. predicted to provoke reactions in no more than 1% of the allergic population). It is acknowledged that moving from ED_{01} to ED_{05} is potentially a significant change and that when COT previously considered the issue of unintended contamination of soya in wheat flour the Committee advised that the limits should not

be relaxed to the ED_{05}. Therefore, the Food Hypersensitivity Policy Team commissioned a review of Codex's full report on threshold levels to understand whether it is appropriate for the recommended reference doses to be applied to regulated allergens in the UK.

4. At the COT meeting last December, it was agreed that a review of Codex's full report was necessary to understand the methods and scientific evidence considered by the Codex Expert Committee. A COT subgroup including some COT members and other external experts was established.

Terms of Reference of the COT subgroup

5. The COT subgroup focussed on the following points, which were included in the terms of reference for their discussions:

Assessment of the Codex Expert Committee report on establishing threshold levels for allergens of global importance. In terms of the allergen thresholds or reference doses (RfDs) recommended for allergens in the report (i.e. walnut, pecan, cashew, pistachio, almond, peanut, egg, hazelnut, wheat, fish, shrimp, milk and sesame):

Are the recommended RfDs based on a robust scientific approach taking into account the questions in the bullet points below? (Please note that some of the reference doses such as those for walnut and cashew are higher than the ED_{05} values).

- Are the data sufficiently representative of the UK population?
- Are there key gaps that need to be addressed before the UK can adopt the recommended RfDs? If so, can they be filled using published literature?
- Is there sufficient evidence to demonstrate that using reference doses based on ED_{05} as opposed to ED_{01} values would not significantly impact upon public health?

COT subgroup assessment approach

6. No formal set methodology was employed for assessment of the Codex Expert Committee report. The COT subgroup met virtually on 4 separate occasions. The subgroup comprised expertise in food allergy and intolerance, food allergy patient and consumer issues, clinical medicine, immunology, toxicology, statistics and analytical methodology. The COT subgroup in addition held a (virtual) discussion with Dr René Crevel, Chair of the Codex Expert Committee.

Summary of the COT subgroup's assessment

Robustness of approach

7. In terms of the question on whether the recommended RfDs are based on a robust scientific approach, the COT subgroup recognised that Codex's full report on threshold levels is from an extremely well qualified Expert Committee. The COT subgroup considered the report to be for the most part, well written. However, the report has not been peer-reviewed, and some limitations were identified, as explained later in this paper.

Representativeness of the data to the UK population

8. In terms of whether the data are sufficiently representative of the UK population, the COT subgroup were of the view that although there are geographic differences in patterns of food allergy, there is no reason to suppose that the data on which the Codex Expert Committee based their analyses are not representative of the UK population.

Data Gaps

9. In addition to the published full report, a webinar on the Joint FAO/WHO Expert Consultation was held in March 2023 where there was opportunity to ask questions. No additional information was provided during the webinar other than that available in the report and any questions raised were answered by reference to the report, as such the only information available for review was the full report and

associated references. After reviewing this, in response to the Terms of Reference question 'In terms of whether there are key gaps that need to be addressed before the UK can adopt the recommended RfDs and whether they can be filled using published literature' the COT subgroup noted the following:

A. Data and modelling to determine ED_{05}

The FAO/WHO Expert Committee employed a 'benchmark dose'/probabilistic hazard assessment approach for defining threshold levels. This 'benchmark dose' approach is different from that used in other areas of toxicology. The COT subgroup felt that this may be appropriate. However, the COT subgroup also felt that insufficient evidence had been provided in the full report to allow an independent critical review of the determination of relevant values and associated uncertainties, or to provide transparency by making the data available for others to analyse it should they wish. They considered that the amount of uncertainty related to ED values might be underestimated. For instance, the modelling methods used are not described in sufficient detail and neither the 'raw' data nor the graphs/figures showing the predicted fit of the models are provided in the report or in the references.

The COT subgroup also noted the analyses relied heavily on two recent papers published by members of the Codex Expert Committee (Remington et al., 2020; Houben et al., 2020). Although these do appear to be the best data available at the present time, there are important associated limitations and uncertainties, including that data vary in quality and quantity across the different allergens. The derived ED values have potential implications regarding the level of protection provided by the recommended RfDs to different populations for different allergens.

Based upon an ED_{05}, five times more people are predicted to have a response than using an ED_{01} (all other things considered equal). But the true ED_{05} and ED_{01} could be appreciably lower (or higher) depending upon the uncertainties associated with the data. Indeed, it was noted by the COT subgroup that the confidence intervals for ED_{05} values are very wide, which

increases the uncertainty and yet there are no detailed analyses of the implications of this, nor any discussion of how this had been taken into account in the recommendations made.

In addition to questions around the accuracy of the modelling of the available data there are uncertainties associated with the applicability of the data for some allergen 'groups', where challenge data are only available for one or a few allergen species and also for some allergic populations, (e.g. for hazelnut allergy, the frequency and type of reaction varies with geographical location related to prevalence of cross-reactive pollen allergies and the study population modelled has a high percentage of patients with pollinosis, who are less sensitive). It is not fully transparent how these biases have been considered, with the Codex Expert Committee stating they have done this by rounding RfDs values but with only a limited description of this.

Another specific area of uncertainty relates to the decision taken to define the ED_{05} for milk. In brief, and as is stated in the report, there is evidence of increased sensitivity in younger children "supported by unpublished data from the Europrevall study showing that children <3.5 years old had consistently (and considerably) lower ED_{10} values than children >3.5 years old." After considering this the Codex Expert Committee went on to recommend using the ED_{05} from Houben et al. (2020) reasoning that *"*However, given that this group is relatively protected from severe outcomes of cow's milk allergy and that intake is easier to control in that group, the expert committee considered that a reference dose based on an ED_{05} derived from the whole population dose-distribution was appropriate." The strength of this argument is questionable and given that milk is a leading cause of anaphylaxis among children, and the single most common cause of fatal anaphylaxis in school aged children in the UK (Baseggio Conrado et. al., 2021) more data are required to fully assess the implication of the decision to recommend the ED_{05} from Houben et. al. (2020) for all product types, some of which could have different population age distributions.

B. Data on severity of reactions

The COT subgroup also noted the uncertainties associated with extrapolating from clinical data to community reactions with regards to the severity of reactions and that there appears to be some inconsistency with respect to the clinical terminology used to describe food allergic reactions of different levels of severity.

The Codex Expert Committee drew heavily on a meta-analysis providing evidence to indicate the same spectrum of severity of reactions at the ED_{01} and ED_{05} for peanut, proposing that data available for other allergens was such that peanut could be considered 'worst case'. The COT subgroup noted, however, that the data analysed were generated in controlled clinical settings with selected well patient populations and that the data on other allergens used to determine if peanut a suitable exemplar case varied greatly in quantity and quality. Additionally, whilst the spectrum of severity may be the same, the COT subgroup noted this still translates to different numbers of reactions of varying severity (5 times more at the ED_{05} versus ED_{01}) and raises questions as to the acceptability, to different stakeholders, of the severity criteria used, which was not covered in the report.

This is particularly important when consideration is given to the fact that thresholds of exposure at which objective reactions are manifest, and the severity of such reactions, will vary with (a) the age of the subject, (b) the time and circumstances of exposure, and (c) be influenced to an uncertain degree by a variety of extrinsic factors such as stress or exercise (acting either individually or collectively). The COT subgroup also found the section on co-factors that can lower reaction thresholds and potentially alter severity of response rather limited, seemingly drawing primarily on data from 3 studies (Dua *et al*. 2019, Versluis *et al*. 2016; 2019). These were studies on adults, allergic to only a few allergens, and either self-reported questionnaire data (Versluis *et al*. studies) or an investigation of a single co-factor (lack of sleep or exercise) at a time (Dua *et al*. 2019), when the Verlsuis *et al*. papers indicate that in almost half of reported reactions more than one co-factor can

be involved.

Thus, although the controlled nature of the clinical studies from which the ED values and severity data are taken is recognised in the report, neither the uncertainties associated with extrapolating to reactions in a community setting, nor the acceptability of the severity criteria used to all stakeholders are considered to be covered in sufficient detail.

C. Analytical capability

The main justifications presented in the Codex Expert Committee's report on the use of RfDs based on ED_{05} values appear to be limitations in the sensitivity of available analytical procedures and the prevention of overuse of PAL.

The COT subgroup noted that analytical capability is considered in the report mainly for final product testing for unintended allergen presence (UAP). The deficiencies and gaps in quantitative allergen analysis, and in sampling protocols, are well outlined in the report and the sub-group concur these gaps should be addressed. Failure to do so risks frustration of analytical verification of allergen quantitative risk assessment. Mistakes in such verification could jeopardise harmonisation of PAL. The COT subgroup also noted that there were publications such as Holzhauser *et al*. (2020), which are not included but that directly address the question of analytical suitability for RfDs and concluded there was capability at least for some allergens. More recently an FSA-funded project, which is due to be published on food.gov.uk, reviewed allergen analytical testing methodologies, measurement parameters and sensitivity of methods available in the UK. These data could be applied to update analytical performance characteristics, particularly Limits of Quantification (LOQ), and the COT subgroup suggest review of these data against threshold concentrations derived from EDx and food intake data (Birot *et al*., 2018). The COT subgroup also noted that analytical capability information is often not in the public domain (albeit it may be available on request from the method kit manufacturers). Thus, there is a further gap in

that much that is captured in the report from the literature may not reflect real-world application. Moreover, the COT subgroup is aware of impending publication of AOAC 'Guidance on Food Allergen Immunoassay Validation' which aims to address some of the problems identified by the report (AOAC, 2023).

The COT subgroup noted that analytical limitations undoubtedly do exist and there may be important international differences in the sophistication of relevant analytical methods. However, in the UK it is technically possible to adopt the more conservative ED_{01} approach where this can be supported by the available analytical methods. Moreover, end product analysis is not the sole means by which allergen quantitative risk assessment can be verified and the subgroup also looked forward to improvements in analytical method performance, including lower LOQs, driven by the Codex Expert Committee report and the COT subgroup's comments upon it.

ED01 versus ED05

10. In terms of the question regarding whether there is sufficient evidence to demonstrate that using the reference doses recommended by the Codex Expert Committee based on ED_{05} as opposed to ED_{01} values would not significantly impact upon public health, the COT subgroup noted that:

- The agreed objective of the Joint FAO/WHO Expert Consultation on allergen thresholds was to minimise the probability of a clinically relevant food allergic reaction to a point where further refinement (reduction) would not materially impact on health (individuals or populations).
- The Codex Expert Committee reported that all symptoms caused by exposure to levels up to ED_{05} fell into a 'mild or moderate' category.
- The Codex Expert Committee concluded that for the eight priority allergens the safety objectives would be met by using the recommended RfDs which are based on ED_{05} rather than an ED_{01} values. RfDs were rounded to one significant figure and some priority allergens with similar ED_{05} values were grouped together.

11. While recognising the valuable work that has been undertaken by the Codex Expert Committee, the COT subgroup had some concerns regarding the adoption of the recommended RfDs based on ED_{05} values from a risk-based perspective. These reservations and other observations are summarised below:

- The COT subgroup acknowledged that Figure 4 on page 50 of the full report shows that in the case of peanuts the spread of symptoms is not very different between ED_{01} and ED_{05}. However, the fact remains that employing RfDs based on ED_{05} would be expected to result in 5-fold more peanut-sensitised subjects experiencing adverse effects following exposure – albeit with generally mild symptoms.
- An example of what the influence of different ED values would have on the frequency of those displaying an allergic reaction is outlined below:

  Example: Children's water ice containing milk present unintentionally: 1 million consumer units on the market in the UK.

  A. Assuming that the product is bought only for children and based upon a prevalence of milk allergy among children of 2-3%, this would result in 20,000-30,000 milk allergic children eating this product.

  B. If PAL was applied to this product based on the ED_{01} value of 0.2 mg, and for purposes of simplicity it is assumed milk is present at this level in all products: ~200-300 children could experience an objective reaction; up to 5% of those developing mild anaphylaxis (10-15).

  C. If PAL was applied based on the ED_{05} value of 2mg, and for purposes of simplicity it is assumed milk is present at this level in all products: ~ 1000-1500 children could experience an objective reaction; up to 5% of those potentially developing mild anaphylaxis (50-75).

  D. Note: the ED_{05} estimated from a single dose study with young children was lower, so the ED_{05} numbers could be higher depending upon the age distribution of the consumers.

12. Taking into account these concerns and the data gaps highlighted above, the COT subgroup were of the view that there is not sufficient evidence to demonstrate

that using the references doses based on ED_{05} as opposed to ED_{01} values would not significantly impact on public health.

13. The subgroup noted that, when considered appropriate, and if there are available appropriate analytical methods, the use of ED_{01} rather than ED_{05} values would afford greater protection to a larger number of subjects with food allergy. In this context 'appropriate analytical methods' are defined as those that are matrix-validated, and that have LOQ and other relevant performance characteristics that provide confidence that ED_{01} reference values can be measured reliably.

Summary of key conclusions

14. In addressing questions posed in the Terms of Reference the COT subgroup reached the following conclusions:

- There is no reason to suggest that the data are not sufficiently representative of the UK population.
- There are uncertainties regarding the way in which ED values have been derived – and as a consequence the accuracy of these values. Given the available data upon which derived ED values are based this is a limitation that must – at present – be acknowledged. However, there are no key gaps that can be filled using the published literature.
- There is insufficient evidence to demonstrate that using reference doses based on ED_{05}, as opposed to ED_{01} values would not significantly impact on public health.

Overall summary

15. The only approach currently available for the identification for food allergen reference values as a basis for PAL is the use of derived ED values. This was the approach adopted by the Codex Expert Committee and by the authors of the published papers upon which the Committee relied. The Codex Expert Committee

has recommended adoption of RfDs based on ED_{05} values for priority allergens. The COT subgroup view is that if derived ED values are going to be adopted then ED_{01} vales, rather that ED_{05} values, would be more protective of those with food allergy. However, the final decision regarding the use of ED values will need to be taken with regard to the availability of suitably reliable and sensitive techniques for the measurement of specific food allergens, potential impacts on the restriction of consumer choice, and the possible unintended consequences of the over-use of PAL.

16. It should be noted, however, that the COT subgroup has some reservations regarding the use of ED values as described in the Codex report and the recent literature on which that report is based. The main concern is that the derived ED values may be less accurate and more imprecise than assumed in the Codex report. The COT subgroup noted that the report summary would have benefitted from an adequate rehearsal of the major caveats, data gaps and uncertainties that have had to be accommodated in reaching their recommendations and that are contained in the body of the report. The COT subgroup identified that the description and interpretation of the statistical methods and the results reported were limited and not sufficient to allow the conclusions drawn by the Codex Expert Committee to be adequately reviewed by interested independent parties.

17. The COT subgroup concluded that currently there is insufficient evidence to demonstrate that using reference doses based on ED_{05}, as opposed to ED_{01} values would not significantly impact on public health. The COT subgroup recommends that the accuracy and reliability of derived ED values should be evaluated more rigorously if they are going to continue to form the basis for determination of reference vales for food allergens.

List of Abbreviations and Technical terms

AOAC	Association of Official Agricultural Chemists
ED	Eliciting Dose
CCFL	Codex Committee on Food Labelling
FAO	Food and Agriculture Organization of the United Nations
FSA	Food Standards Agency
LOQ	Limit of Quantification
PAL	Precautionary allergen labelling
RfD	Reference dose
UAP	Unintended Allergen Presence
WHO	World Health Organization

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