EFSA supporting publication 2014:EN-696

TECHNICAL REPORT

Outcome of a public consultation on the draft Scientific Opinion of the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) on the evaluation of allergenic foods and food ingredients for labelling purposes[1]

European Food Safety Authority[2,3]

European Food Safety Authority (EFSA), Parma, Italy

ABSTRACT

The European Food Safety Authority (EFSA) carried out a public consultation to receive input from the scientific community and all interested parties on the draft scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes, prepared by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) and endorsed by the Panel for public consultation at its Plenary meeting on 10 April 2014. The written public consultation for this document was open from 23 May 2014 to 08 August 2014. EFSA received comments from 30 interested parties. EFSA and its NDA Panel wish to thank all stakeholders for their contributions. The current report summarises the outcome of the public consultation, and includes a brief summary of the comments received and how the comments were addressed. The NDA Panel prepared an updated version of the Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes taking into account the questions/comments received. The opinion was discussed and adopted at the NDA Plenary meeting on 30 October 2014, and is published in the EFSA Journal.

KEY WORDS

food allergy, prevalence, allergens, methods of detection, eliciting dose, thresholds, food labelling, public consultation, outcome

[1] On request from EFSA, Question No EFSA-Q-2014-00248, approved on 20 November 2014.

[2] Correspondence: nda@efsa.europa.eu

[3] Acknowledgement: EFSA wishes to thank the members of the Working Group on Food Allergy: Roberto Berni Canani, Sébastien La Vieille, Hendrik van Loveren, Martinus Løvik, Rosangela Marchelli, Martin Stern, Stephan Strobel and Dominique Turck for the preparatory work on this output and the members of the Panel on Dietetic Products, Nutrition and Allergies (NDA) for their contribution to this output.

Suggested citation: European Food Safety Authority, 2014; Outcome of a public consultation on the draft Scientific Opinion of the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) on the evaluation of allergenic foods and food ingredients for labelling purposes. EFSA supporting publication 2014:EN-696. 202 pp.

Available online: www.efsa.europa.eu/publications

TABLE OF CONTENTS

BACKGROUND

With the benefit of experience gained since 2004[4] and based on the allergens listed in the annex of Commission Directive 2007/68/EC except for lactose, the Food Safety Authority of Ireland requests that EFSA provides a scientific opinion on:

- The prevalence of each allergy in the European Union.
- Recommendations for threshold concentrations of each allergen in food that would provide an acceptable level of protection for at-risk consumers;
- The suitability, or otherwise, of qualitative and quantitative DNA-based tests (PCR) for the detection and quantification of food allergens in comparison with immunological (e.g. ELISA) or other methods.

TERMS OF REFERENCE

In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments from the scientific community and stakeholders, EFSA shall release the draft Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes for public consultation. The comments resulting from the public consultation shall be published in a technical report. Before its adoption by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel), the draft Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes may need to be revised, taking into account the comments received during the public consultation.

[4] Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission relating to the evaluation of allergenic foods for labelling purposes (Request N°EFSA-Q-2003-016) (adopted on 19 February 2004).

CONSIDERATION

1. Introduction

Following a request from the Food Safety Authority of Ireland, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) drafted a scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. In line with EFSA's policy on openness and transparency, and in order for EFSA to receive comments on its work from the scientific community and stakeholders, EFSA engages in public consultations on key issues. Accordingly, the draft scientific opinion was published on EFSA's website for comments (23 May 2014 to 08 August 2014) (see Appendix A). The NDA Panel prepared an updated version of the scientific opinion, taking into account the comments received. The updated scientific opinion was discussed and adopted at the NDA Plenary meeting on 30 October 2014, and is published in the EFSA Journal (EFSA NDA Panel, 2014). EFSA is committed to publishing the comments received during the public consultation, as well as a short report on the outcome of the consultation.

2. Screening and evaluation of comments received

2.1. Comments received

EFSA received 274 comments from 30 interested parties, including universities, medical and other expert societies, research consortiums, governmental and non-governmental organisations, patient associations, the food industry and food industry associations.

Table 1: List of organisations submitting comments

Organisation	Country
AFDIAG-Association Francaise des Intolérants au Gluten	FR
Anaphylaxis Campaign	UK
Bioseutica B.V.	NL
Coeliac UK	UK
DANONE	FR
Deutscher Allergie- und Asthmabund	DE
EAACI: European Academy of Allergy and. Clinical Immunology	UK
EuroCommerce	BE
European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	BE
Faculty of Medicine, NANCY France - Consultant in the Allergy Department Hospital Center EPINAL	FR
Familles rurales	FR
FEDIOL	BE
Food & Drink Federation	UK
Food Standards Agency	UK
FoodDrinkEurope	BE
Interassociation des personnes allergiques et intolérantes	FR
Interest Group on Food Allergy - Sociedade Portuguesa Alergologia Imunologia Clinica	PT
International organisation of vine and wine (OIV)	FR
Italian Coeliac Association	IT
Biodiagnostics	UK
National Food Institute, Technical University of Denmark	DK

Organisation	Country
Nutrition Counselling	DE
R-Biopharm AG	DE
SPAIC: Portuguese Society of Allergology and Clinical Immunology	PT
The Allergen Bureau Ltd	AU
The Danish Veterinary and Food Administration	DK
The iFAAM FP7 Project	UK
TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	NL
Università del Piemonte Orientale A. Avogadro, Italy	IT
VITAL Scientific Expert Panel (VSEP)	AU

AU, Australia; BE, Belgium; DE, Germany; DK, Denmark; FR, France; IT, Italy; NL, the Netherlands; PT, Portugal; UK, the United Kingdom.

A summary of the comments is given below, and all written comments received are listed in Appendix B. Several parties submitted identical comments.

2.2. General comments

2.2.1. Scope and interpretation of the terms of reference

The scope and Terms of Reference (ToR) of the present opinion have been generally misunderstood by stakeholders. EFSA acknowledges that its tasks as risk assessment body in the field of allergen labelling may not have been clearly communicated to stakeholders. In order to address this aspect, section 1 of the opinion (introduction) has been expanded to include EFSA's interpretation of the ToR and a detailed explanation of EFSA's remit in this field, as suggested by several comments received, as follows:

"1. Introduction and interpretation of the terms of reference

It is EFSA's role to provide risk managers (European Parliament, European Commission and Member States) with scientific and technical support in order to inform management decisions regarding the adoption and implementation of EU legislation in relation to the labelling of foodstuffs. This includes information to be provided to consumers on allergenic foods and food ingredients that may pose a health risk to sensitive individuals.

Current EU legislation indicates in Annex II of Regulation (EU) No 1169/2011 a list of substances subject to mandatory labelling that can cause allergies or intolerances in sensitive individuals upon oral consumption. Labelling of allergenic foods and ingredients listed in Annex II is mandatory when: (i) they are intentionally added in the manufacturing of foodstuffs; and (ii) they are still present in the final product to be delivered to the consumer. In this regulatory context, it is EFSA's task to provide risk managers with relevant scientific and technical information relative to these substances and their capacity to induce allergic reactions in sensitive individuals.

However, it is not EFSA's task to decide:

- *whether certain substances should be added to, or removed from, the list of ingredients subject to mandatory labelling;*
- *on the labelling of substances listed in Annex II when unintentionally present in foods (precautionary labelling);*
- *whether allergic reactions induced by these substances by mechanisms other than oral ingestion (e.g. skin contact, inhalation) should be considered for risk management purposes.*

The terms of reference (ToRs) specify that, with the benefit of the experience gained since 2004 and based on the allergens listed in the annex (Annex IIIa) of Commission Directive 2007/68/EC (Annex II of Regulation (EU) No 1169/2011), except for lactose, the Food Safety Authority of Ireland requests that EFSA provides a scientific opinion on:

- *the prevalence of each allergy in the EU;*
- *recommendations for threshold concentrations of each allergen in food that would provide an acceptable level of protection for at-risk consumers; and*
- *the suitability, or otherwise, of qualitative and quantitative DNA-based tests (polymerase chain reaction, PCR) for the detection and quantification of food allergens in comparison with immunological (e.g. enzyme-linked immunosorbent assay, ELISA) or other methods.*

In order to address the ToRs, the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA Panel) decided to update its previous opinions (EFSA, 2004, 2006a, 2006b) relative to food ingredients or substances with known allergenic potential listed in Annex IIIa of Directive 2003/89/EC, as amended, keeping in mind that:

- *Prevalence data from the EU-funded multidisciplinary Integrated Project EuroPrevall and from other ongoing research projects relevant to this task will become available only in the next few years. In this context, EFSA launched a procurement project (CT/EFSA/NDA/2012/02) on literature searches and reviews related to the prevalence of food allergy in Europe to gather prevalence data on food allergy in the general (unselected) population (University of Portsmouth, 2013). Details about the literature search and the criteria used to select pertinent studies are depicted in the technical report (University of Portsmouth, 2013).*
- *The NDA Panel will provide an overview of the current methodologies used for allergen risk assessment as well as information on the aspects that could be taken into account by risk managers when establishing threshold concentrations for allergens in foods for labelling purposes. The NDA Panel will also summarise published eliciting dose levels calculated for populations (or population thresholds) that have been derived for some allergenic foods. It is not EFSA's responsibility to decide which level of protection is "acceptable" for risk managers, consumers and/or other stakeholders, and therefore it is not in the NDA Panel's remit to establish concentrations of allergens in food for labelling purposes.*
- *The NDA Panel will also address the suitability, or otherwise, of qualitative and quantitative DNA-based tests (PCR) for the detection and quantification of food allergens in comparison with immunological (e.g. ELISA) or other methods, including mass spectrometry. The NDA Panel will provide risk managers with relevant information about:*
  - *the characteristics of each method available and the current use;*
  - *the possibilities of combining more than one method for the analysis of allergenic ingredients in foods; and*
  - *the factors which should be considered when selecting one or the other method for a particular purpose.*

Examples of the use of different methods for the detection of a given allergenic food or ingredient in different matrices will be given when available. However, the NDA Panel does not aim to provide an exhaustive list or a compilation of all publications available in this field, nor to decide or recommend the best method or test for the detection or quantification of each particular allergen. The selection of the method or methods for the detection/quantification of allergens in foodstuffs would largely depend on the food targeted for analysis (e.g. food matrix, level and method of processing, quantity and form of the allergenic ingredient expected to be present) and the purpose of the analysis (e.g. screening, quantification).

The NDA Panel wishes to clarify that the present opinion does not aim to be a textbook on food allergy or an exhaustive compilation of the clinical symptoms, diagnostic methods and/or clinical management of food allergy, not to guide choices on infant feeding practices or clinical decisions in the management of food-allergic individuals. However, general information about the above-mentioned aspects is given to risk managers to put into context the clinical implications of management decisions in the labelling of food allergens".

2.2.2. Comments related to risk management

EFSA would like to highlight that the following comments are considered to be related to risk management rather than to risk assessment and should therefore be addressed to the European Commission and Member States. They are not further discussed in the present report and were not taken into account to update the draft scientific opinion released for consultation, except for the inclusion in section 1 of a detailed explanation of EFSA's remit in this field.

- Comments related to the current legislation on the labelling of allergenic foods and food ingredients and other information to be provided to consumers, including:

  i) whether certain substances should be added to, or removed from, the list of ingredients subject to mandatory labelling,

  ii) the labelling of substances listed in Annex II of Regulation 1169/2011 when unintentionally present in foods (precautionary labelling),

  iii) the labelling of allergenic foods and food ingredients to which subjects allergic to substances listed in Annex II of Regulation 1169/2011 could react (cross-reactivity).

- Comments related to food fraud and mechanisms in place for food analysis and quality control by enforcement authorities.

- Comments related to the mislabelling or inappropriate labelling of food products in the market (e.g. foods in the market not complying with the mandatory labelling of foods/ingredients listed in Annex II of Regulation 1169/2011) or to labelling practices which may be misleading for the consumer (e.g. simultaneous labelling of a product as "gluten free" and "not suitable for coeliac patients").

- Comments related to the socioeconomic impact of modifying labelling practices or to the impact of abolishing precautionary labelling on the quality of life of food allergic patients.

2.2.3. Comments related to literature searches, criteria for the selection of relevant information, and incomplete datasets

Questions were received in relation to the literature searches undertaken to retrieve pertinent data for this opinion (e.g. search terms, search date, and criteria for study selection).

EFSA launched a procurement project (CT/EFSA/NDA/2012/02) on literature searches and reviews related to the prevalence of food allergy in Europe to gather prevalence data on food allergy in the general (unselected) population (University of Portsmouth, 2013). Details about the literature search and the criteria used to select pertinent studies are depicted in the technical report (University of Portsmouth, 2013). The NDA Panel used the technical report as a basis to summarise data on the prevalence of food allergy in unselected populations.

Literature searches to retrieve information for other sections of the opinion were undertaken up to September 2013 by experts of the Working Group on Food Allergy and by the Nutrition Unit. Given the long list of allergenic foods/ingredients covered and the complexity of all aspects addressed

(allergens identified, methods of detection, effects of food processing on allergenicity, cross-reactivity, minimum observed eliciting doses), systematic literature searches were not undertaken.

The vast majority of the scientific references which have been identified by stakeholders as major omissions in the opinion were published during or after September 2013. The NDA Panel will specifically consider these publications in the revision of the opinion where appropriate (see specific comments below). However, the Panel notes the large number of scientific publications related to one or more aspects of this opinion which are published every month, and that the results of several ongoing research projects could provide relevant information for its update, as suggested in some of the comments received.

2.2.4. Comments related to the inclusion of additional references regarding the methods for the detection and/or quantification of allergenic foods/ingredients

A number of comments were received by a stakeholder in relation to virtually all sections of the opinion dealing with the detection of specific allergenic foods/ingredients in foodstuffs. Such comments refer to reference methods of detection/quantification exclusively developed by a company and/or requesting to remove some references from the text, considering that they may promote products developed by commercial competitors. In some cases, direct reference to the commercial name of methods or kits developed by the company was requested.

As stated in Section 1 of the revised opinion (introduction and interpretation of the terms of reference), *examples of the use of different methods for the detection of a given allergenic food or ingredient in different matrices will be given when available. However, the NDA Panel does not aim to provide an exhaustive list or a compilation of all publications available in this field, nor to decide or recommend the best method or test for the detection or quantification of each particular allergen. The selection of the method or methods for the detection/quantification of allergens in foodstuffs would largely depend on the food targeted for analysis (e.g. food matrix, level and method of processing, quantity and form of the allergenic ingredient expected to be present) and the purpose of the analysis (e.g. screening, quantification).*

2.2.5. Comments related to eliciting dose (ED) values for populations in relation to each individual allergenic food/ingredient

Comments were received in relation to a number of sections dealing with specific allergenic foods/ingredients (e.g. Sections 14-26) regarding ED and threshold values for populations which have been derived for each particular allergenic food/ingredient. The Panel wishes to clarify that, as specified in lines 2653-2655 of the published draft opinion, the sections of the opinion dedicated to specific allergenic foods/ingredients will only address minimum (observed) eliciting doses for individuals reported in challenge studies, rather than estimated thresholds for populations. This clarification has been moved to the end of Section 12.2 (determination of thresholds for an individual), as follows: "*Minimum (observed) eliciting doses for individuals reported in oral challenge studies for specific allergenic foods/ingredients will be addressed in the remaining sections of this Opinion, clearly specifying whether they refer to objective reactions, to subjective reactions, or both. Doses will be reported as in the original publications, i.e. as amount of food or as mg of protein, and conversion factors will not be used to transform one into the other, unless specified by the authors*".

Eliciting doses for populations (ED*p*) and thresholds for populations are collectively discussed in Section 12 of the opinion (allergen risk assessment and determination of "thresholds for allergenic foods/ingredients), both in general and specifically for allergenic food/ingredients for which data are available. Similarly, all comments received regarding ED*p* and population thresholds for individual allergenic foods/ingredients will be addressed collectively in Section 2.3.12 of the present technical report.

2.2.6. Comments related to the selection of individual oral challenge studies to derive minimum (observed) eliciting doses

Comments were received in relation to almost every section of the opinion dealing with specific allergenic foods/ingredients, questioning how the Panel selected the studies described in the sub-sections dedicated to minimum (observed) eliciting doses (MEDs). Some inconsistencies were pointed out. For example, it was noted that papers reporting on MEDs for several allergenic foods (Blom et al., 2013) were only considered in the specific sections for some allergens (milk, egg, peanut, cashew nut), but not for others (hazelnut, walnut, soy). Similarly, it was questioned why some references reporting on MEDs for milk (Patriarca et al., 2002), eggs (Meglio et al., 2013), hazelnut (Flinterman et al., 2006), shrimp (Atkins et al., 1985; Nordlee et al., 2013) and sesame (Morisset et al., 2003), were not included in the opinion. In this context, a definition of "adverse reaction" was requested (e.g. considering whether a reaction is subjective or objective, and its severity). It was also requested to consistently report the type of adverse reactions noted in the individual studies, and whether the doses to which subjects reacted were expressed as amount of protein or as amount of food.

The Panel took as a basis to identify pertinent human studies which had reported on MEDs for specific allergenic foods the publications by Allen et al. (2014) and Taylor et al. (2014), quoted in the draft opinion as Allen et al., 2013 and Taylor et al., 2013, because they were only published ahead of print at the time the Panel had access to them for the preparation of the draft opinion. The studies by Patriarca et al. (2002) and Morisset et al. (2003) have already been considered and quoted in the draft opinion within the MEDs sections for milk and sesame, respectively. The study by Nordlee et al. (2013) was published as an abstract only and does not provide sufficient information for a scientific evaluation of MEDs for shrimp. It reports collectively on MEDs from threshold-finding DBPCFCs conducted in 24 subjects (original data) plus 24 subjects from unspecified published studies. The publication by Flinterman et al. (2006) was not considered by Allen et al. (2014) and Taylor et al. (2014), but has been considered by the Panel to update the section on nuts. The suggested references reporting on MEDs for eggs (Meglio et al., 2013) and shrimp (Atkins et al., 1985) have been taken into consideration when updating the sections on MEDs in relation to these allergenic foods for completeness, as well as MEDs reported by Blom et al. (2013) for soy, walnut and hazelnut.

The Panel acknowledges that, as stated by some stakeholders, guidelines to perform oral challenges (in particular double-blind, placebo-controlled, food challenges (DBPCFCs)), including a scoring system of symptoms and criteria to be used for considering a challenge as positive on the basis of the number, type and/or severity of the reactions observed (objective) or reported (subjective), have been issued in the last years (Sampson et al., 2012). The Panel also acknowledges that, even if this information was not available to the Panel at the time of the preparation of the draft opinion, a symptom severity scoring system is being developed in the context of the Europrevall project in order to support the analysis of threshold distribution doses (Defernez et al., 2013). However, the Panel notes that the majority of the studies available reporting on MEDs do not define the requirements used to classify allergic reactions on the basis of the amount, type (subjective/objective) and/or severity of the symptoms experienced by subjects following oral challenges, and that there is no consensus on a severity scoring system to rank symptoms. Therefore, MEDs for both subjective and objective reactions, regardless of their severity, have been reported for individual studies in the draft opinion. The draft opinion has been revised and updated to indicate clearly and consistently throughout whether MEDs refer to subjective or objective (MOEDs) reaction, or both. With respect to whether the doses (MEDs) to which subjects reacted were expressed as amount of protein or as amount of food, the Panel decided to report on MEDs as in the original papers. Amounts of food were not converted into amounts of protein or vice-versa, if this information was not indicated in the paper. As specified in Section 2.2.5 of this technical report, this clarification has been incorporated in the revised version of the opinion at the end of Section 12.2 (determination of thresholds for an individual).

2.3. Specific comments

The main scientific issues raised in the comments received are summarised below, together with the way in which the Panel addressed these comments. The NDA Panel has reviewed all comments

carefully and has updated the scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes accordingly, when appropriate. The updated scientific opinion is published in the EFSA Journal (EFSA NDA Panel, 2014).

2.3.1. Introduction

Comments received

1. There was a question on whether data on the prevalence of food allergy in Europe from Europrevall was already available.

Panel consideration of comments received

Ad 1. As stated in the draft opinion, prevalence data from Europrevall had not been published and were not available to EFSA. One of the comments received clarifies that such data will become available in the next years.

2.3.2. Classification of adverse reactions to foods and definition of terms

Comments received

2. There was a request to include in this section definitions of different types of "thresholds", and of the severity of allergic reactions to food.

3. It was suggested to align the definitions given in this section 2 and the classification of adverse reactions to food with the recently published guidelines of the European Academy of Allergy and Clinical Immunology (EAACI).

Panel consideration of comments received

Ad 2. These terms are introduced in Section 12 of the revised opinion.

Ad 3. Definitions regarding the classification of adverse reactions to food have been aligned with the recently published guidelines of the EAACI, and the suggested reference (Muraro et al., 2014b) has been quoted in the opinion.

2.3.3. Clinical symptoms of food allergy

Comments received

4. A number of editorial changes have been proposed in this section. Also, the message conveyed in page 20, lines 884-889, was found unclear.

5. It has been proposed to estimate of the relative proportions of reactions associated with each symptom, which could help to assess the public health impact.

6. It was pointed out that the description of the Heiner syndrome, although correct, should not be included under the heading of asthma.

7. More clarity was requested regarding the symptoms of food allergy which could be attributed to IgE and non IgE-mediated (or cell-mediated) food allergy.

8. It was requested to include the symptoms associated with laryngeal oedema.

9. It was suggested to include a section on exercise induced food allergies after Section 3.1.1. on urticaria and angioedema, on the basis of an increased frequency of these symptoms following physical exercise in combination with intake of alcohol and certain drugs.

10. There was a request to mention the "new entity" of semi-delayed anaphylaxis to mammal meats by sensitization to alpha-galactose.

11. It was questioned whether the last paragraph of the introduction in Section 3 was in line with the conclusions of the Scientific Opinion of the EFSA's Panel on Food Additives, Flavourings, Processing Aids and Food Contact Materials (AFC) on the assessment of the results of the study by McCann et al. (2007) on the effect of some colours and sodium benzoate on children's behaviour. The paragraph read: "*The food allergic nature of some clinical syndromes such as migraine, attention deficit hyperactivity disorder, and irritable bowel syndrome is still controversial. There is some published evidence that, in a small proportion of individuals, exposure to certain foods or preservatives may be the underlying trigger (Carter et al., 1993; McCann et al., 2007)".*

12. A request was made to include contact dermatitis and asthma triggered by skin contact and airborne food allergens, respectively, as occupational diseases linked to the handling of foods in the work place.

Panel consideration of comments received

Ad 4. The editorial changes suggested have been introduced in this section. The paragraph originally in page 20, lines 884-889, has been deleted in the revised version of the opinion.

Ad 5. The Panel notes that very few studies have addressed the prevalence of symptoms in allergic patients at the population level, that most publications refer to retrospective studies in populations recruited in tertiary centres, and that the diagnostic criteria of food allergy as well as the description of clinical symptoms are very heterogeneous. Therefore, the Panel considers that the available literature does not allow the relative proportions of reactions associated with each symptom in food allergic patients in the general population to be estimated. No changes were introduced in the opinion on the basis of this comment.

Ad 6. The Heiner syndrome is now described on its own (i.e. not included under asthma).

Ad 7. The Panel considers that attributing an immune mechanism to each sign and symptom with which allergic reactions to food manifest is not scientifically possible. Although academically classified as IgE-mediated, cell-mediated and mixed, allergic reactions to food manifest with signs and symptoms which may vary over time and which cannot be attributed univocally to one or other mechanism. No changes were introduced in the opinion on the basis of this comment.

Ad 8. Symptoms associated with laryngeal oedema have been described in Section 3.3.3.

Ad 9. Exercise-induced food allergy is already addressed within the sections corresponding to the symptoms triggered by exercise in conjunction with food ingestion (3.1.1. Urticaria and angioedema; 3.5. Generalised symptoms-anaphylaxis). No changes in the opinion were deemed necessary on the basis of this comment.

Ad 10. The following paragraph has been inserted at the end of Section 3.5. (severe reactions-anaphylaxis) in the revised version of the opinion: *"A novel IgE-mediated reaction to a mammalian oligosaccharide epitope, galactose-alpha-1,3-galactose (alpha-gal), has been described in adult patients in association with delayed onset anaphylaxis, angioedema and urticaria 3-6 h after ingestion of mammalian meat (e.g. beef, pork and lamb). The symptoms can be severe and may require epinephrine injections and care in emergency departments (Commins et al., 2009). Tick bites appear to be the route of sensitisation. Patients with specific IgE antibodies to alpha-gal continue to emerge, particularly among children (Kennedy et al., 2013)".*

Ad 11. It was not the intention of the NDA Panel to suggest that food additives are responsible for attention deficit hyperactivity disorders in children, but rather to highlight that allergic reactions to foods and food ingredients have been hypothesised to be involved in the development of clinical syndromes of unknown cause. The last sentence of the paragraph has been removed from the final version of the opinion to avoid confusion.

Ad 12. Allergic reactions to food NOT triggered through the oral route (i.e. food ingestion) have not been specifically addressed because they are out of the scope of this opinion. However, examples of allergic reactions triggered by inhalation during, for example, steam cooking of foods are given within the sections devoted to particular allergenic foods/ingredients, where appropriate, to illustrate that very low allergen doses can trigger severe allergic reactions.

2.3.4. Diagnosis of food allergy

Comments received

13. It was stated that the paper by Grimshaw et al. (2003) cited in Section 4.2.3 devoted to skin prick tests was incorrectly cited, as it referred to the effect of food matrices containing different concentrations of fat on the threshold of reactivity in food challenges.

14. It was pointed out that recent papers regarding European guidelines for the diagnosis of food allergy (Muraro et al., 2014b), and for the standardisation of protocols for oral challenges (Sampson et al., 2012), as well as a systematic review regarding the accuracy of tests (SPT and specific serum IgE antibodies) for the diagnosis of food allergy (Soares-Weiser et al., 2014) were not considered in the opinion.

15. Available tests other than RAST (e.g. Immunocap) were missed in Section 4.2.2. on the measurement of specific serum IgE antibodies.

16. There were comments suggesting that all food allergic children should be evaluated for bronchial hyper-reactivity, since lethal acute asthma may also occur in food-allergic, non-asthmatic patients.

17. It was stated that, in several cases, sensitization is associated with objective symptoms, and therefore component-resolved diagnoses (CRD) does provide such information. An example of sensitization to Cor a 9 and Cor a 14 being highly specific for a severe hazelnut allergy in Dutch children and adults was provided (Masthoff et al., 2013).

Panel consideration of comments received

Ad 13. The paper by Grimshaw et al. (2003) is intentionally quoted in Section 4.2.3. to make the point that since the food matrix has a marked effect on the reactions experienced after allergen ingestion, the presentation of allergens within the food matrix during an SPT challenge also needs to be carefully considered. No changes were introduced in the opinion on the basis of this comment.

Ad 14. These recently published papers have been considered by the Panel in revising the opinion. The following sentence has been inserted at the end of Section 4.2.1. on food challenges: *"Guidelines for the diagnosis of food allergy and consensus papers aiming for the standardisation of oral challenge protocols have been recently published in Europe (Muraro et al., 2014b) and the United States (Sampson et al., 2012)".*

The last sentence of the conclusions (Section 4.3.) has been amended accordingly to read: *"The Panel notes that there is a need for standardisation of derived allergens for SPT. The Panel also notes that guidelines aiming for the standardisation of oral challenge protocols*

in order to facilitate epidemiological and other multicentre studies on allergic reactions to foods are now available".

Soares-Weiser et al. (2014) has been quoted when discussing the role of SPTs and levels of specific serum IgE antibodies in the diagnosis of food allergy (Sections 4.2.2. and 4.2.3.).

Ad 15. The description of ImmunocapISAC has been moved from Section 4.2.7 to Section 4.2.2. The Panel wishes to clarify that other methods based on existing technical principles are constantly being developed, and that a detailed discussion on these is beyond the scope of this opinion.

Ad 16. As stated in the introduction of the revised version of the opinion (Section 1), the Panel wishes to clarify that the present opinion does not aim to be a textbook on food allergy or an exhaustive compilation of the clinical symptoms, diagnostic methods and/or the clinical management of food allergy, nor to guide choices or clinical decisions in the management of food allergic individuals. No changes were introduced in the opinion on the basis of this comment.

Ad 17. Although sensitive, CRD is not very specific for the diagnosis of food allergy, although the specificity of CRD may vary depending on the offending allergen (Soares-Weiser et al., 2014). The Panel considered that no changes were needed in this general part of the opinion on the basis of this comment.

2.3.5. Management of food allergy

Comments received

18. Regarding the following paragraph in Section 5.1 (allergen avoidance) of the published draft opinion: "*Mothers of exclusively breastfed food allergic infants (i.e. with clinical diagnosis of food allergy) are also advised to eliminate the offending foods from their diet, since breast milk may contain the allergen in amounts able to trigger an adverse reaction in their infants and maintain the underlying disease process (Machtinger and Moss, 1986)"*, it was questioned whether this statement for which an "old" reference was quoted was in contradiction with current guidelines for the dietary management of food allergy (Burks et al., 2011; Muraro et al., 2014a).

19. Some comments indicated that, whilst early studies using oral immunotherapy are encouraging, quality of the evidence base is questionable and the treatment is often associated with adverse effects. It was also noted that de Silva et al. (2014) identified that further research was required to explore whether the benefits of treatment continue after the intervention is stopped, as data in this regard are especially sparse. On the other hand, it was pointed out that recent work on acquiring peanut tolerance through oral exposure was not covered in this section.

Panel consideration of comments received

Ad 18. The Panel notes that the above-mentioned guidelines refer to breast-feeding practices in at-risk infants for the primary prevention of food allergy, a topic which is discussed in Section 7.1.1.3. in line with these guidance documents. However, these guidance documents do not refer to breast-feeding practices in infants with a clinical diagnosis of food allergy, which is the issue discussed in Section 5.1. (allergen avoidance in the management of diagnosed food allergy). The Panel considers that no changes are needed in the opinion on the basis of this comment, except for the addition of the recently published paper by Muraro et al. (2014a) in Section 7.1.1.3. More recent references on breastfeeding practices in food allergic infants have been inserted at the end of the paragraph (Isolauri et al., 1999; Koletzko et al., 2012).

Ad 19. As stated in Section 5.2.1. of the published draft opinion, the Panel agrees that the long-term efficacy, safety and cost-effectiveness of specific oral tolerance induction require further assessment and that specific oral tolerance induction is not yet recommended in routine practice as a means to induce tolerance in children with IgE-mediated food allergy. The reference by de Silva et al. (2014) has been added to the text and adequately covers recent literature on peanuts.

2.3.6. Epidemiology of food allergy

Comments received

20. There were some comments asking for clarity regarding the prevalence data given in the opinion, particularly in relation to the type of populations studied (e.g. unselected populations *versus* clinic patients) and in relation to the methods used to assess prevalence (e.g. self-reported, sensitisation, and food challenge). Two references of recent publication were suggested for inclusion in the opinion (Nwaru et al., 2014a; Nwaru et al., 2014b). These comments were accompanied by the observation that few (and inconclusive) studies assessed time-trends, and that increased self-reported prevalence over time may be the result of over-reporting due to increased awareness.

21. Several parties highlighted the German anaphylaxis register as a valuable source of data for estimating the prevalence of severe allergic reactions and anaphylaxis.

22. It was unclear why prevalence data for allergic reactions to foods/ingredients not listed in Annex IIIa of Directive 2003/89/EC, as amended, was given in the opinion, being outside the ToR. It was also unclear why prevalence data was depicted for these and not for other foods with allergenic potential. In this context, it was questioned whether the conclusions in Section 6.5 could be read as a suggestion to add new foods/ingredients to Annex IIIa.

Panel consideration of comments received

Ad 20. In the draft opinion published for consultation, it was specifically mentioned (lines 1107-1109) that "*only prevalence data for the general population or for age-specific subgroups within the general (unselected) population, rather than data obtained in subjects selected based on their disease risk or disease condition, will be considered whenever available"*. It was also specifically stated, both in the general part and in all sections devoted to particular allergenic foods, whether the prevalence estimates given were based on self-reported, sensitisation (specific IgE antibodies or positive SPT), or oral challenge studies. As mentioned before, details on the systematic literature searches conducted, the inclusion and exclusion criteria applied for the selection of the studies, and data from all studies available classified by age group, type of allergenic food, and method used to estimate the prevalence of food allergy, is publicly available (CT/EFSA/NDA/2012/02) (University of Portsmouth, 2013). In addition, the original studies identified by the suggested references are largely the same as those quoted in the draft opinion and identified by the contractor. However, the Panel acknowledges the added value of the meta-analytic prevalence estimates reported in the recent publications (Nwaru et al., 2014a; Nwaru et al., 2014b) and the geographical comparisons made across European regions, and these have been taken into account to update different sections of the opinion dealing with the prevalence of food allergy in Europe.

The Panel agrees with the consideration that few (and inconclusive) studies (mostly patient-based) have assessed time-trends in the prevalence of food allergy, and that the increased self-reported prevalence over time may be the result of over-reporting due to increased awareness. This concept was already expressed in Section 6.3. of the draft opinion and no changes were considered necessary on the basis of that comment.

Ad 21. A paragraph reporting data from the anaphylaxis registry of German speaking countries has been inserted in Section 6.4., as follows:

"A total of 197 anaphylactic reactions (defined as severe systemic allergic reactions with concomitant pulmonary and/or cardiovascular symptoms) were registered between 2006 and 2009 in the anaphylaxis registry of German speaking countries in children and adolescents (Hompes et al., 2011). Food allergens accounted for 58% of cases. Legumes (n = 36), and in particular peanuts (n = 26), were the most frequent food allergens causing severe allergic reactions, followed by tree nuts (n = 29), cow's milk (n = 11) and hen's egg (n = 8)".

Ad 22. The literature search (University of Portsmouth, 2013) did not aim specifically to retrieve papers on the prevalence of allergy to any particular food not listed in Annex IIIa; data was rather extracted from available papers reporting on the general prevalence of food allergy in Europe and incorporated in the draft opinion for completeness. It was not the intention of the Panel to suggest or imply that these and not other foods with allergenic potential should be considered by risk managers for mandatory labelling. However, the Panel acknowledges that reporting prevalence data for some allergenic foods not in Annex IIIa (and thus not in the ToR) may be interpreted as such, and therefore Section 6.5. has been deleted from the opinion.

2.3.7. Influence of environmental and individual factors in the distribution of food allergies

Comments received

23. It has been highlighted that no reference is made in the draft opinion to the recently published EAACI guidelines for the management of food allergy in relation to breastfeeding and feeding practices in infants (Section 7.1.1.3). Reference has also been made to ongoing studies aiming to gather data on the impact of early introduction of allergenic foods into the diet of infants and young children (e.g. LEAP, EAT, PEAD, and HEAP).

24. It was suggested to delete Section 7.1.2. on food preparation and processing with the argument that these are not environmental factors and are anyway addressed in Section 10.

25. Comments were received highlighting that some factors (e.g. genetic background, age and sex) were discussed at some length, while others (e.g. food processing, hygiene hypothesis, microbial exposure) were discussed less, despite the rather large number of publications and the importance of the postulated influences. On the other hand, it was noted that the available evidence about risk factors for food allergy is inconclusive and inconsistent (Nwaru et al., 2014a), and that there is little evidence to affirm that food consumption patterns or the abundance of an allergen in food play a role in the prevalence of food allergy.

26. It was suggested to include the filaggrin mutation among the genetic factors with a putative role in modifying the prevalence of food allergy. It was also noted that different routes of exposure, such as inhalation and/or skin contact, and potential sensitisation to food proteins, were not discussed in this section.

Panel consideration of comments received

Ad 23. The Panel reiterates that, although not quoted specifically because of only recent publication, the text in Section 7.1.1.3. is fully in line with the EAACI guidelines for the primary prevention of food allergy in relation to breastfeeding and feeding practices in infants (Muraro et al., 2014a). This reference has been added to the revised version of the opinion, but no changes were needed in the text. The Panel also notes that although ongoing studies may provide new data on this topic in the near future, such data are not yet available and thus no changes were introduced in the opinion on the basis of this comment.

Ad 24. Food preparation and processing are only briefly indicated as environmental factors to be considered when assessing the prevalence of food allergy. The Panel considers that this section should be kept as short as it is to avoid overlap with Section 10. The opinion was not changed on the basis of this comment.

Ad 25. As discussed above, the role of food preparation and processing was kept short to avoid overlap with section 10. A paragraph has been added at the end of section 7 to clarify the context of the following sub-sections, as follows: "*Although several environmental and individual factors have been proposed as potential modifiers of the risk of developing food allergy, there is inconsistency across studies regarding the factors investigated and the results obtained (Nwaru et al., 2014a). Examples of environmental and individual factors which have been proposed to influence the distribution of food allergies are briefly discussed below"*. Indeed, the purpose of this section is only to highlight the multiplicity of factors which could affect the distribution of food allergy across populations and age groups citing some examples, rather than to review systematically all the literature addressing them or to imply that they have a role in the development of food allergy in all circumstances. Another paragraph has been added at the beginning of Section 7.2 to take into consideration the systematic review which has been recently published: *"Sex, age, family history of atopy and the presence of other allergic diseases are among the individual factors considered important in the development of food allergy (Nwaru et al., 2014a)".*

Ad 26. The following paragraph has been inserted at the end of Section 7.2.1. on genetic background: "*Mutations in the profilaggrin gene resulting in loss of function of filaggrin, an epidermal protein with a role in the skin barrier function, have been identified as a risk factor for developing allergic sensitisation, atopic eczema, and allergic rhinitis, as well as asthma in individuals with atopic eczema (van den Oord and Sheikh, 2009). Fewer studies have reported on the relationship between filaggrin loss-of-function (FLG-LOF) mutations and risk of food allergy (Brown et al., 2011). It has been suggested that FLG-LOF mutations could modulate the risk of food allergy through early sensitisation to food allergens due to the impairment of the skin function barrier (Filipiak-Pittroff et al., 2011; Venkataraman et al., 2014)*".

2.3.8. Characterisation of food allergens

Comments received

27. Line 1465: It was noted that PDB-files is an acronym for Protein Databank files, and not for Program Data Base files.

28. Lines 1526-1529: It was noted that lipid transfer proteins are responsible for most of the ***severe*** reactions to the *Rosaceae* family.

29. It was argued that the section of immunological characterisation did not make the pertinent and important point that immunological characterisation only provides information about antigenicity, but not about allergenicity.

30. It was suggested to comment on functional methods for the immunological characterisation of food allergens.

31. There was a request to mention the role of components other than protein, such as lipids, in determining the allergenic potential of allergenic foods (Bublin et al., 2014).

32. It was pointed out that several relevant allergens outside the four main allergen protein superfamilies were left aside in Section 8.3.1. and that several allergenic proteins and carbohydrate moieties (e.g. ovalbumins, ovomucoids, transferrins, β-lactoglobulin, alpha-

galactose in the development of allergy to meat products) were not mentioned in Section 8.3.2.

33. Section 8.6.2, which referred to the use of mass spectrometry for the molecular characterisation of food allergens, was found confusing, incomplete and imprecise.

Panel consideration of comments received

Ad 27. Program Data Base files has been replaced by Protein Databank files (PDB-files) in the revised version of the opinion.

Ad 28. The sentence has been modified as follows: "*Lipid transfer proteins are frequent and potentially severe allergens: they are one of the numerous defence protein families (also called pathogenesis-related proteins) that are responsible for most of the* ***severe*** *allergic reactions to fruits from the Rosaceae family*".

Ad 29. Lines 1734-1736 of the draft opinion clearly stated that the IgE-binding capacity of a protein is related to its antigenicity, and not necessarily to its allergenicity upon ingestion. This point has been further clarified in the revised opinion, as follows: "*The Panel notes that the IgE-binding capacity of a protein is related to its antigenicity (i.e. the ability to combine specifically with the final products of the immune response, e.g. specific IgE), and not necessarily to its allergenicity upon ingestion (i.e. the ability to trigger immune-mediated clinical reactions)".*

Ad 30. The following sentence has been added to Section 8.7 (immunological characterisation of food allergens) on functional immunological tests:*"Functional immunological tests, such as the basophil activation test (BAT), have been used for the characterisation of food allergens with inconsistent and variable results. These methods cannot replace other immunological tests".*

Ad 31. The Panel notes that the role of lipids in determining the allergenic potential of proteins is largely speculative (Bublin et al., 2014). No changes were introduced in the opinion on the basis of this comment.

Ad 32. The Panel wishes to clarify that the aim of Sections 8.3.1 and 8.3.2 (allergens of plant and animal origin, respectively) is not to provide an exhaustive list of all individual allergens identified, but to introduce the superfamilies under which most allergens are classified on the basis of their origin, structure and function. The individual allergens identified for each allergenic food in Annex IIIa are listed and described within the section devoted to that allergenic food (e.g. ovalbumin and ovomucoid are listed in Section 16.3, under allergy to eggs). No changes were introduced in the opinion on the basis of this comment.

Ad 33. In the draft opinion, the general (non allergen-specific) use of MS methods was described primarily in two sections: Section 8.6.2. (Allergen identity and identification of epitopes) and Section 11.1.3. (detection of allergens by Mass Spectrometry). The information contained in these sections has been re-organised in the revised opinion to improve clarity. Section 8.6.2. (allergen identification: sequencing and Mass Spectrometry) is devoted to the two strategies available for the identification of proteins by MS: the "bottom-up" and the "top-down" approaches. Details on the use of MS for the qualitative/quantitative determination of food allergens are given in Section 11.1.3., which summarises the MS methods used for allergen quantification at the protein level (Section 11.1.3.1.), and at the peptide level (Section 11.1.3.2.). For the latter, tagging methods, the isotopically labelled synthetic peptide method and label-free methods are described under specific headings for clarity. The identification of epitopes, previously in section 8.6.2, is now described in Section 8.6.3. on its own.

2.3.9. Cross-reactivities

Comments received

34. Comments were received about the labelling provisions of rapeseed protein as a novel food ingredient in relation to its capacity to induce adverse allergic reactions in mustard allergic individuals.

35. It was suggested to take into consideration the cross-reactivity between mammalian meats due to galactose-alpha-1,3-galactose.

36. It was found that the sentence in line 1765 of the draft opinion "*Pollen allergens (e.g. birch pollen, mugwort) cross-react with LTP, ubiquitous in plants, and with profilins*" was not clear.

Panel consideration of comments received

Ad 34. As stated in Section 2.2.2 of this technical report (comments related to risk management), it is not under EFSA's remit to decide on the labelling of allergenic foods and food ingredients to which subjects allergic to substances listed in Annex II of Regulation 1169/2011 could react (cross-reactivity). This decision is under the competence of risk managers (European Commission and Member States).

Ad 35. A new paragraph on semi-delayed anaphylaxis following ingestion of mammal meats by sensitization to alpha-galactose has been inserted in Section 3.5 of the revised opinion (see Ad 10). However, mammalian meats are not listed in Annex IIIa and thus will not be addressed further. No changes were introduced in the opinion on the basis of this comment.

Ad 36. Lines 1761-1775 of the draft opinion have been re-organised as follows for clarity:

> *"Examples of highly cross-reacting allergen groups are the profilins and the LTPs, both generally regarded as panallergens (Bonds et al., 2008). Panallergens are defined as homologous molecules that originate from a multitude of organisms and cause IgE cross-reactivity between evolutionary unrelated species (Hauser et al., 2010).*
>
> *Food allergy may occur following sensitisation to inhaled allergens, such as pollen. An example is the so called "pollen-food allergy syndrome", which usually manifests as OAS, although systemic symptoms may occur. Many patients allergic to birch pollen become allergic to apples, hazelnuts, celery and carrots. These patients have specific IgE antibodies to Bet v1 or Bet v2 (profilin), the major birch pollen allergens.*
>
> *nsLTP have been identified in most plant-derived foods and in pollen from several plants. Sensitisation to nsLTP is characterised by geographic differences. While in the Mediterranean countries allergy to Rosaceae fruits is mostly associated with sensitisation to nsLTPs, in Northern Europe it is more often associated with sensitisation to birch pollen (Bet v 1). However, the co-presence of specific cross-reacting antibodies in patients' serum does not indicate which came first: the pollen allergy or the food allergy (Hauser et al., 2010). Cross-reactions are also observed between pollen of Compositae (mugwort) and celery".*

2.3.10. Effects of food processing on allergenicity

Comments received

37. It was found that this section was not complete, and that effective cross-reference to other sections of the opinion (i.e. devoted to specific allergenic foods) would help.

38. It was requested to clarify the use of the term "allergenicity" in the introduction to Section 10 (i.e. ability to induce sensitisation or to trigger reactions?).

39. Within Section 10, it was found that the formation of advanced glycation-end products (AGE) should be specifically mentioned.

40. It was requested to comment on acidic hydrolysis under enzymatic hydrolysis and on the effects of gluten deamidation in inducing the formation of peptides capable of eliciting severe allergic reactions (Denery-Papini et al., 2012).

41. In the section devoted to enzymatic hydrolysis (10.2), it was requested to include as an example studies investigating the residual allergenicity of hydrolysed infant and follow-on formulas, and to refer to the American standards for a formula to qualify as hypoallergenic.

42. It was asked whether "*typically, loss of tertiary structure is followed by (eventually reversible) unfolding*" (line 1821 of the draft opinion) should read "*typically, loss of tertiary structure is followed by (eventually **irreversible**) unfolding*".

43. It was requested to explain what high hydrostatic pressure (HHP) processing is in more detail.

44. There were comments stating that certain processing methods which are known to reduce the allergenic potential of foods/ingredients (e.g. extraction procedures and refinement of oils), had not been specifically mentioned in Section 10, but only within the sections devoted to specific allergenic foods/ingredients. It was suggested to include a brief description of these methods in Section 10.

Panel consideration of comments received

Ad 37. As stated in the last paragraph of the introduction to Section 10 in the draft opinion, "*this section provides an overview of the most common methods of food processing and their effects on the allergenic potential of foods*", whereas "*the specific alterations induced by processing on foods/ingredients included in Annex IIIa of the Directive 2003/89/EC (as amended) are reported in the dedicated sections*". Indeed, the aim of this section is to illustrate how food processing can affect the allergenicity of foods in general, and to describe briefly the most common methods used for cooking/manufacturing foodstuffs which can affect allergen structure and function, and thus allergenicity. Examples are only given for illustrative purposes in this section. The effects of food processing on the allergenicity of specific allergenic foods and ingredients are covered in detail in Sections 13 to 27 of the opinion. No changes were introduced in the opinion on the basis of this comment.

Ad 38. The terms **immunogenicity** (i.e. the ability to induce a humoral and/or cell-mediated immune response), **antigenicity** (i.e. the ability to combine specifically with the final products of the immune response, e.g. specific IgE antibodies) and **allergenicity** (i.e. the ability to induce allergy and/or trigger an allergic reaction) have been defined in the first paragraph of Section 2 (classification of adverse reactions to foods and definition of terms) of the revised opinion. It has also been clarified that, in the context of this opinion, the term **allergenicity** will be restricted to the ability to trigger an allergic reaction, and will not refer to the ability to induce allergy, as follows:

> ***"Immunogenicity** denotes the ability to induce a humoral and/or cell-mediated immune response, whereas **antigenicity** refers to the ability to combine specifically with the final products of the immune response, e.g. specific IgE antibodies. In this Opinion, the term **allergenitic**y (i.e. the ability to induce allergy and/or trigger an allergic reaction) will be restricted to the ability to trigger an allergic reaction, and will not refer to the ability to induce allergy".*

The draft opinion has been revised where appropriate for a consistent use of the above-mentioned terminology.

Ad 39. The last sentence of the first paragraph in Section 10 has been modified as follows: "*In addition, thermal processing can generate new immunologically reactive structures (neoallergens), among which the advanced glycation-end products (AGE) produced by the Mailard reaction of amino groups of proteins with sugars (Mills et al., 2009). Thermal processing can also destroy existing epitopes by cleavage of the protein (Davis and Williams, 1998)".*

Ad 40. A new sub-section on chemical hydrolysis (Section 10.2.2) has been added to the opinion as follows:

"***10.2.2. Chemical hydrolysis***

Chemical hydrolysis under acid or alkaline conditions has seldom been used in industrial processes, mostly in combination with heat and high hydrostatic pressure (HHP) treatments. Wheat protein hydrolysates produced by either enzymatic or acid treatments are commercially available. The latter were shown to contain peptides with lower MW than the former, and to be less antigenic (Akiyama et al., 2006). Also chemically hydrolysed salmon had a reduced or abolished IgE-binding capacity (Sletten et al., 2010). The clinical significance of these findings is to be established.

Deamidation is an industrial way to modify the protein structure for increasing solubility by chemical hydrolysis. Gluten proteins are deamidated to enhance their solubility and technological applications. Severe allergic reactions have been reported after the consumption of food products containing deamidated gluten in subjects tolerant to wheat (Denery-Papini et al., 2012). The sera of these patients displayed IgE binding to deamidated γ- and ω2-gliadins and deamidated total gliadins, generally at high concentrations".

Ad 41. Section 7.1.1.3. (introduction to food and breast feeding), within the context of environmental factors affecting the distribution of food allergy (i.e. food consumption), already addresses the issue of the lack of EU regulatory definition regarding the level of protein hydrolysation in formulas. The effect of enzymatic processing on the allergenicity of infant formula is already addressed in sub-section 15.5.2. (within the section devoted to allergy to milk and dairy products). No changes were introduced in the opinion on the basis of this comment.

Ad 42. The sentence *"typically, loss of tertiary structure is followed by (possibly reversible) unfolding*" is correct. No changes were introduced in the opinion on the basis of this comment.

Ad 43. Section 10.4 on HHP has been slightly expanded for clarity and more examples have been added, as follows:

"*HHP processing is a non-thermal technology which allows homogeneity of treatment throughout the food product on account of the fact that the applied pressure is uniformly distributed within the HHP chamber, regardless of the size and shape of the product. It only affects non-covalent bonds, such as the hydrogen, ionic and hydrophobic bonds, thus exerting a substantial impact on the tertiary and quaternary structures of the protein, inducing denaturation and conformational changes.*

HHP shows a variety of effects on food allergens depending on the protein structure, the pressure applied (100-400 MPa in general), the temperature and the duration of the treatment. High pressure treatments may reduce the allergenicity of a protein by different mechanisms: by protein denaturation, by induction of conformational changes (thus

destroying conformational epitopes), by making linear epitopes more accessible to digestive enzymes, and by allergen removal (extraction into the medium).

In HHP-treated rice grains in distilled water, the reduced amount of allergenic proteins in rice was attributed to the release of these proteins from the grains into the aqueous solution (Estrada-Girón et al., 2005). In soy sprouts obtained from HHP-treated seeds, the reduced immunoreactivity was explained by a higher availability of the HHP-treated proteins for enzymatic hydrolysis during germination (Peñas et al., 2011). In contrast, Kleber et al. (2007) found that antigenicity of β-lactoglobulin in whey protein isolate increased with an increase of pressure (200 to 600 MPa), temperature (30 to 68 °C) and duration of the treatment (10 to 30 min). This effect may be due to unfolding of the protein, with exposure of epitopes previouslyburied within the protein structure (Mills and Mackie, 2008). The potential utility of HPP processing for reducing allergenicity of foods is reported in a review (Huang et al., 2014)".

Ad 44. The Panel agrees with this comment. A new section (10.5) has been introduced in the opinion describing how extraction procedures and the degree of refinement affect the protein content and the allergenicity of oils.

"10.5. Methods for the production of oils

Methods for the extraction of oils from seeds/fruits/fish affect the presence of proteins in the final product, and thus their eventual allergenicity. Cold pressed extraction, thermal pressed extraction, and extraction with different solvents have a different impact on the amount of proteins present in oil. The crude oil can be refined following different subsequent steps: degumming, neutralising, bleaching and deodorising, each step potentially reducing the amount of protein in the final product.

Few data exist on the effect of different methods for oil refining on total residual protein content. Crude oils may contain 100 times more proteins than refined oils (Crevel et al., 2000). However, the reported protein content in crude oils varies substantially depending on the method used for protein determination. The Panel notes that the protein content of refined oils, and hence their allergenicity, strongly depends on the type of processing and the degree of refinement of the oil".

How the methods of extraction of other lipidic materials (e.g. lecithins) affect allergenicity are described in the sections dedicated to specific allergenic foods/ingredients (e.g. egg and soy).

2.3.11. Methods for the detection of allergens and allergenic ingredients in food

Comments received

45. Several comments were made on the normalisation of analytical results obtained by different ELISA kits, and requested to consider the recently published paper by Johnson et al. (2014).

46. It was requested to mention the limitations of lateral flow devices (LFDs).

47. There was confusion among some stakeholders regarding the difference between reference materials and certified reference materials (CRMs).

48. It was pointed out that the distinction between direct methods capable of detecting allergenic proteins and indirect methods able to detect DNA had not been addressed in the draft opinion.

49. It was noted that food processing may affect the relative recovery of DNA and allergenic proteins, which could lead to false positive or negative results.

50. There were requests to indicate in the opinion (e.g. in Table 2) the context in which different methods of detection/quantification could be used (e.g. screening, research, and analysis for regulatory enforcement) and whether/in which circumstances these methods could be used in combination as complementary.

51. It was requested to clarify the role of mass spectrometry in the detection and quantification of allergenic food/constituents in foodstuffs.

Panel consideration of comments received

Ad 45. A new paragraph has been inserted in Section 11.1.1.1. (Enzyme Linked Immunosorbent Assay), which reads as follows: "*Normalisation of results obtained by different ELISA kits has been proposed by applying experimental Food Analysis Performance Assessment Scheme (FAPAS) proficiency tests. It was shown that the use of a standardised calibrant (e.g. a matrix-matched standard) can be successfully used to normalise the data set from different allergen ELISA kits (Sykes et al., 2012). More recently, a dessert matrix incurred with pasteurised egg white or skimmed milk powder was produced and evaluated in a multi-laboratory trial as a promising quality control material for food allergen analysis (Johnson et al., 2014)*".

The paper by Johnson et al. (2014) has also been considered for the revision of the ELISA methods available for milk and egg.

Ad 46. The following clarification has been added at the end of Section 11.1.1.2. (lateral flow devices and dipsticks): "*They* [LFDs] *are inexpensive, quick, portable, and easy to use, but are only qualitative or semi-quantitative (LOD ca 1 mg/kg), and suffer from all limitations described for ELISA (e.g. matrix interference, inter- and intra-assay variations, batch-to-batch variations, etc.). They are mainly used for a preliminary screening".*

Ad 47. Lines 2024-2026 of the draft opinion have been revised as follows for clarity: "*Very important for the quantification of allergens is the availability of certified reference materials (CRMs). Reference materials developed by different producers are commercially available for most major food allergens. However, the analytical results obtained using these reference (but not certified) materials may differ depending on the type of allergen/antibody and the procedures used to obtained them".*

Ad 48. The Panel notes that the distinction between direct methods capable of detecting allergenic proteins and indirect methods able to detect DNA of the allergenic food had been made very explicitly in the draft opinion, both in Section 11 (including the conclusions, Section 11.4.) and in the sections devoted to specific allergenic foods/ingredients. No changes were introduced in the opinion on the basis of this comment.

Ad 49. The importance of the recovery of both allergenic proteins and DNA from processed foods has already been addressed in the draft opinion (Section 11.3. Detection of allergens and allergenic ingredients in processed foods). It was also noted that DNA extraction from lipophilic matrices (e.g. fats and oils) with low amounts of DNA, and from complex matrices containing surfactants and emulsifiers is sometimes difficult (see last paragraph of Section 11.2). For clarity, it has been added that this may lead to false negative results. It has also been clarified in the revised version of the opinion (Section 11.2.1. PCR) that "*Some foods may contain compounds that are PCR inhibitors, such as polyphenols, so that it is necessary to carry out a preliminary extraction of these compounds before DNA amplification. False positive results due to improper choice of primers or similarity of the sequence to be amplified with other species are less frequent".*

Ad 50. Although not mentioned in Table 2, it was generally indicated in the text whether the methods described could be used for the detection and/or the quantification of allergenic food/ingredients, specifying which methods could be used for routine diagnostics and which methods were mostly used for research purposes. Whenever two methods are complementary, this is clearly indicated in the opinion. It is not in EFSA's remit to indicate which methods of analysis should be used for regulatory enforcement.

Ad 51. The Panel acknowledges that the explanation of the role of mass spectrometry in the detection and quantification of allergenic food/constituents in foodstuffs suffered from being addressed in two different sections: Section 8 concerning the characterisation of allergens and Section 11 related to the methods of detection of allergenic foods and food ingredients, causing some confusion. As indicated in Ad 33, the information contained in these sections has been re-organised in the revised opinion to improve clarity. Section 8.6.2. (allergen identification: sequencing and Mass Spectrometry) is devoted to the two strategies available for the identification of proteins by MS: the "bottom-up" and the "top-down" approaches. Details on the use of MS for the qualitative/quantitative determination of food allergens are given in Section 11.1.3., which summarises the MS methods used for allergen quantification at the protein level (Section 11.1.3.1.), and at the peptide level (Section 11.1.3.2.). For the latter, tagging methods, the isotopically labelled synthetic peptide method and label-free methods are described under specific headings for clarity.

2.3.12. Determination of thresholds for allergenic foods/ingredients

Comments received

52. Section 12 (determination of thresholds for allergenic foods/ingredients) was found confusing by most stakeholders. The scope was unclear (several comments on this section related to risk management issues, which are outside EFSA's remit), as well as the meaning of the word "threshold". The message conveyed in this section was found inappropriate, as well as the description of the existing methodology for allergen risk assessment.

53. There were requests to mention previous experiences in the labelling of allergens unintentionally present in foods in other countries (e.g. current "regulatory thresholds" being used in Switzerland or Japan).

54. Comments were received requesting to characterise "adverse reactions" on the basis of the severity of signs/symptoms.

55. The selection of the literature cited in this section was questioned, e.g. a thesis by Remington (2013) was quoted, but not the work based on Europrevall data (Defernez et al., 2013). In addition, the Appendix reporting data on eliciting doses for populations (ED*p*) was found unclear. On the one hand, it was mentioned that some publications included sub-sets of data used by others. On the other, it was unclear why the lower 95% CI of ED_{05}, instead of ED_{05}, were reported in some cases.

Panel consideration of comments received

Ad 52. The Panel acknowledges that Section 12 of the draft opinion could have been difficult to understand in the absence of a clear definition of terms and a clarification on the interpretation of the ToR. Section 12 has been re-named, re-arranged and expanded to clarify and describe in more detail current knowledge in allergen risk assessment.

Ad 53. In Switzerland and Japan, "thresholds" for allergen labelling (same concentration in foods for all allergenic food/ingredients) have been established without considering available data on individual or population thresholds. In addition, there are no data on the impact of such

labelling practices on the food allergic population. No changes were made in the opinion on the basis of this comment.

Ad 54. As explained in Section 2.2.6 of this technical report, the Panel acknowledges that, as stated by some stakeholders, guidelines to perform oral challenges (in particular double-blind, placebo-controlled, food challenges (DBPCFCs)), including a scoring system of symptoms and criteria to be used for considering a challenge as positive on the basis of the number, type and/or severity of the reactions observed (objective) or reported (subjective), have been issued in recent years (Sampson et al., 2012). The Panel also acknowledges that, even if this information was not available to the Panel at the time of the preparation of the draft opinion, a symptom severity scoring system is being developed in the context of the Europrevall project in order to support the analysis of threshold distribution doses (Defernez et al., 2013). However, the Panel notes that the majority of the studies available reporting on MEDs do not define the requirements used to classify allergic reactions on the basis of the amount, type (subjective/objective) and/or severity of the symptoms experienced by subjects following oral challenges, and that there is no consensus on a severity scoring system to rank symptoms. In Section 12, it has been indicated whether objective reactions, subjective reactions, or any reaction, were used to estimate ED*p* or probability threshold distributions in different studies.

Ad 55. The NDA Panel was not aware of the publication by Defernez et al. (2013) at the time of the preparation of the draft opinion. However, ED_{10} estimated using Europrevall oral challenge data have been discussed in the revised version of the opinion and incorporated in the Appendix. However, details on the DBPCFCs for specific allergenic foods conducted within the Europrevall project have not been published yet to the Panel's knowledge, and thus these studies will not be considered specifically within the sections on MEDs dedicated to specific allergenic foods/ingredients.

The Appendix now includes ED*p* calculated from distributions of individual threshold data from different studies. For those estimated within the context of VITAL 2.0, the thesis by Remington (2013) was preferred to the published papers (Allen et al., 2014; Taylor et al., 2014) because it reports ED_{01}, ED_{05} and ED_{10}, rather than only those used as basis to derived reference doses. It has also been clarified in the text that the thesis is the preparatory work for the two other publications (Allen et al., 2014; Taylor et al., 2014), and that it took into account data from all publications cited in the Appendix, except for Eller et al. (2012).

2.3.13. Coeliac disease

Comments received

56. It was requested to refer to two articles reporting on collaborative studies regarding the use of the R5 sandwich ELISA and the R5 competitive ELISA, respectively, for the detection and quantification of gluten in foods.

57. It was pointed out that the use of the monoclonal antibody G12 for the detection of gluten by ELISA had been omitted in the draft opinion.

58. It was noted that no details were given regarding the use of lateral flow devices (LFDs) for the qualitative detection of gluten in foods.

Panel consideration of comments received

Ad 56. The R5 sandwich ELISA and the R5 competitive ELISA which have been developed for the detection and quantification of gluten in foods had been already described in the draft opinion on the basis of the original publications describing the development of these methods. No changes were introduced in the opinion on the basis of these comments.

Ad 57. The use of the monoclonal antibody G12 for the detection of gluten by ELISA is described in the revised version of the opinion (Section 13.5.1.1.) as follows:

"Another antibody, G12 mAB, raised against the toxic 33-mer from α-gliadin as a detection antibody together with the antibody A1 as a capture antibody, was applied in both sandwich and competitive ELISA assays with high sensitivity. The LOD for gliadin was 0.6 mg/kg in the sandwich format and 0.44 mg/kg in the competitive format. Thus, the LOD for gluten in the competitive format (obtained by multiplying prolamin concentrations by 2) was < 1 mg/kg. The method can be applied to both native and partially hydrolysed cereals (Moron et al., 2008). In a collaborative study, it has been shown that the G12 sandwich ELISA method can quantify gluten in foods with a LOD of 4.3 mg gluten/kg of food with good to sufficient precision in the 20-100 mg/kg range also in complex matrices (e.g. chocolate cake) (Don et al., 2014)."

Ad 58. The following sentence has been added to the text in Section 13.5.1.2. (lateral flow devices and dipsticks): "*A LFD which utilises the R5 mAB is able to recognise prolamins in wheat, rye and barley with a LOD of 2.5 mg/kg (Immer and Haas Lauterbach, 2010)".*

2.3.14. Allergy to cereals containing gluten

Comments received

59. One party noted that it is still under discussion whether avenin can be potentially dangerous to coeliac patients.

Panel consideration of comments received

Ad 59. The Panel wishes to clarify that this section is about immune IgE-mediated reactions to cereals, and not about coeliac disease, which has been addressed in Section 13 of the opinion.

2.3.15. Allergy to milk and dairy products

Comments received

60. It was indicated that the publication by Patriarca et al. (2002) was not included in Section 15.7. despite providing information on minimum observed eliciting doses (MOEDs) and this was put as an example of lack of clarity regarding the criteria used for study selection.

61. It was requested to modify the first sentence in Section 15.8. "*Milk is a common cause of allergic reactions in childhood*" to clarify that allergic reactions are triggered by bovine milk proteins and that allergic reactions to CMPs do not occur in the majority of the children population, as could be implied by the wording of the sentence.

62. Comments were made regarding the effect of enzymatic hydrolysis and deamidation on the allergenic potential of infant formula.

63. It was requested to specify that different ELISA kits target different milk proteins, and to consider a recently published validation study (Johnson et al., 2014).

64. It was suggested to include Blom et al. (2013) among the studies providing individual MEDs for milk.

Panel consideration of comments received

Ad 60. The publication by Patriarca et al. (2002) was indeed considered in Section 15.7. of the draft opinion and quoted (lines 3531-3532) among the studies considered which reported on MOEDs. No changes were made in the opinion on the basis of this comment.

Ad 61. For clarity the sentence has been changed to read: "*Cow's milk proteins are common triggers of allergic reactions to food in children*".

Ad 62. These comments have already been addressed in Ad.40 and Ad.41 (section 2.3.10 of this technical report).

Ad 63. The first paragraph of Section 15.6.1 (ELISA) in the draft opinion has been modified as follows:

"Numerous competitive and sandwich ELISA kits for the detection of milk-derived allergens are commercially available, with sensitivity down to 1 mg/kg (Poms et al., 2004a). Some kits detect BSA, casein, and BLG separately, whereas others detect whole milk or whey proteins with LODs between 0.1 and 5 mg/kg. Monoclonal and more suitable polyclonal antibodies have been used against either BLG or casein".

A new paragraph has also been added to Section 15.6.1, as follows:

"A dessert matrix incurred with different amounts of milk protein (as skimmed milk powder) was evaluated as a quality control material for allergen analysis in a multi-laboratory trial (Johnson et al., 2014). Analyses were performed with five ELISA kits based on casein, five kits based on β-lactoglobulin, and one based on total milk. Allergen levels were calculated by using calibration curves and reporting units were converted into mg/kg of skimmed milk powder protein. In general, ELISA kits based on casein were more accurate, while all kits detected milk protein at the 3 mg/kg level. When considering the ISO criteria, only one kit based on casein accurately determined milk protein at 6 and 15 mg/kg against the target value. This study confirms the variability among different commercially available ELISA kits in their ability to quantify the amount of milk protein in complex foods and the need for CRMs, and possibly incurred CRMs".

Ad 64. The study by Blom et al. (2013) has been already considered in the section on MEDs. However, the description of the study has been expanded as follows:

"In a tertiary centre in the Netherlands, 93 children were challenged through a DBPCFC with CMPs at doses of 0.2 mg (mucosal), 1.8 mg (dose 1), and five additional doses up to 1 750 mg of protein (cumulative dose 2 190 mg). Both objective and subjective reactions were recorded. 6 % of children reacted to the first dose of 0.2 mg of protein and 9 % to the first oral dose of 1.8 mg of protein (Blom et al., 2013). In children with IgE-mediated CMA, MEDs for subjective reaction have been reported to be, on average, two to six times lower than for objective reactions (Blom et al., 2013)".

2.3.16. Allergy to eggs

Comments received

65. A request was made to include a reference in page 83, line 3609, to illustrate why the prevalence of sensitisation rates in adults was higher than other countries.

66. It was suggested to include breast milk as an alternative route of sensitisation to egg in page 84, line 3676.

67. It was pointed out that in Regulation (EU) No. 579/2012, in conjunction with Regulation (EU) No. 1234/2007 article 120g and the International organisation of vine and wine (OIV) guidelines 502/2012 based on 427/2010, there exists an analytical threshold for casein and ovalbumin in wine at 0.25 mg/L. Wines treated with casein or ovalbumin products and proven below this limit of 0.25 mg/L have not to be labelled for egg or milk.

68. It was also brought up that ELISA methods appear to be more sensitive and appropriate (i.e. suitable for the analysis of several samples) than MS for the analysis of egg and milk products in wine, as recommended by the OIV.

69. Given the poor performance of ELISA kits in wine, it was requested to consider HPLC or the microbiological testing method inhibition zone on agar plates as the analytical method of choice to establish the LOD for lysozyme in wine.

70. It was requested to consider a recently published validation study of ELISA kits for the detection and quantification of egg proteins in foods (Johnson et al., 2014).

71. It was pointed out that the publication by Meglio et al. (2013) was omitted in the draft (in Section 16.7), despite containing information of MOEDs for egg.

Panel consideration of comments received

Ad 65. The reference (Bakos et al., 2006) has been added to the text to clarify the study for which the data was reported.

Ad 66. Breast milk has not been included among other routes of sensitisation to eggs, besides their direct introduction into the diet, because breast milk is a dietary route, and not an alternative, non-oral route of sensitisation. No changes were introduced in the opinion on the basis of this comment.

Ad 67. The Panel acknowledges that it is not in the scope of this opinion to comment on the conditions under which exemptions from labelling have/have not been granted. Reference to the labelling requirements of wine regarding egg white proteins has been removed from the opinion.

Ad 68. The Panel notes that the sensitivity of the method is not always the most important aspect to consider in the detection of allergenic ingredients in foodstuffs. ELISA methods can be very sensitive but sometimes unreliable, given the complexity of the matrix (wine) and the differences among commercial ELISA kits. MS methods for the analysis of egg and milk products in wine are more robust and analytically more accurate. However, ELISA methods are indeed more suitable for screening purposes, whereas MS methods can be used for confirmation. No changes were introduced in the opinion on the basis of this comment.

Ad 69. It was reported in the draft opinion that lysozyme was efficiently detected and quantified in milk and cheese by using a RP-HPLC-FLD (LOD 8.2 mg/kg)(Pellegrino and Tirelli, 2000). It was also reported that the HPLC-FLD method for lysozyme in milk and dairy products, which was published as an ISO standard, was successively modified and validated (Schneider et al., 2010), and that the HPLC method coupled to MS has been applied for detecting residual egg proteins (ovalbumin, ovomucoid and lysozyme) in red wine fined with a commercial egg white preparation (Tolin et al., 2012). The use of the microbial-based approach is not quantitative and is generally considered as obsolete. No changes were introduced in the opinion on the basis of this comment.

Ad 70. A description of the study by Johnson et al. (2014) has been included in Section 16.6.1.1. (ELISA) as follows:

"A dessert matrix incurred with different amounts of egg protein from pasteurised egg white was evaluated as a quality control material for allergen analysis in a multi-laboratory trial (Johnson et al., 2014). Analyses were performed with five commercial ELISA kits. Estimation of egg protein concentrations varied among the different kits. Only one kit was able to detect the target level of the incurred egg protein in the dessert matrix, which gave the exact concentration of the incurred allergen only at the 3 mg/kg level".

Ad 71. The study by Meglio et al. (2013) has been included in the section of MEDs as follows:

"Threshold-finding DBPCFCs with raw hen's egg were conducted in 20 children with IgE-mediated, challenge-confirmed hen's egg allergy undergoing desensitization therapy (Meglio et al., 2013). Oral, liquid doses of 0.05 g, 0.1 g, 0.3 g, 0.6 g, 1.3 g, 2.5 g, 6.3 g and 14 g of egg white protein were given every 15 min. The test was terminated when either signs (objective) or symptoms (subjective) arose. Five children reacted to the first dose tested".

2.3.17. Allergy to nuts

Comments received

72. It was noted that the first paragraph of Section 17.4.1 (cross-reactivity among nuts and between nuts and peanuts), which read "*Allergy to nuts is almost exclusively induced by non pollen-mediated food sensitisation. Only allergy to hazelnut can be due to sensitisation to birch pollen or, less frequently, to mugwort pollen (Hirschwehr et al., 1992; Caballero et al., 1997)*" was incorrect and relied on relatively old literature for nuts.

73. It was noted that information available on MEDs from Blom et al. (2013) on walnuts and hazelnut, and from Flinterman et al. (2006) on hazelnut, was not considered in the opinion.

74. It was questioned the approach of "combining" threshold dose information for the different nuts without giving a rationale for this.

Panel consideration of comments received

Ad 72. The paragraph has been modified as follows: *"Allergies to nuts are generally induced by non pollen-mediated food sensitisation. However, allergy to hazelnut, almond and, less frequently, other nuts can be induced by sensitisation to birch pollen, plane tree pollen or mugwort pollen (Vieths et al., 2002; Flinterman et al., 2006)".*

Ad 73. Data from Blom et al. (2013) on walnuts and hazelnut, and from Flinterman et al. (2006) on hazelnut, have been considered in section 17.7 on MEDs, as follows:

"In another DBPCFC study, 28 children sensitised to hazelnut were challenged with increasing doses of defatted hazelnut flour in series: 10 µg, 100 µg, 500 µg, 1 mg, 10 mg, 100 mg, 300 mg, 1 g, and 3 g (protein content, 15.5%). Only 12 children were diagnosed with hazelnut allergy by DBPCFC. Of these, four reported OAS at doses starting at 1.6 mg of hazelnut protein (MED) and eight developed an objective reaction. The MOED was 46.5 mg of hazelnut protein.

DBPCFCs were conducted in 31 cashew nut allergic, 28 hazelnut allergic, and 13 walnut allergic children (Blom et al., 2013). Challenges started with 0.2 mg of protein applied to the oral mucosa and continued with six oral, increasing doses (in mg of protein) until a subjective or an objective reaction occurred (first dose was 1.7 mg for hazelnut, 1.8 mg for walnut, and 2.3 mg for cashew nut). Among cashew nut allergic children, 10% reacted to the mucosal challenge and 3% to the first oral dose. Among hazelnut allergic children, 0.4% reacted to the mucosal challenge and 15% to the first oral dose. The MOED for walnut was 0.9 mg of protein".

Ad 74. Information on MEDs for different nuts was given separately in the draft opinion, and not "combined". However, the conclusion that "Data from DBPCFCs shows that minimum doses of nuts eliciting allergic reactions in susceptible individuals may be below 1 mg of protein" applies to all (i.e. objective reactions observed for hazelnut, walnut and cashew nut at the first dose tested in the mg range). No changes were introduced in the opinion on the basis of this comment.

2.3.18. Allergy to peanuts

Comments received

75. It was stated that the evidence which suggests a difference in the allergenicity of roasted versus boiled peanuts is of academic interest, but in practical terms it has no utility in Europe, as there are no boiled peanuts in this market.

76. Some stakeholders found that the sentence at the end of the MEDs section "*However, few data are available on the doses that may trigger allergic reactions in highly sensitive patients, who are often excluded from challenge tests but tend to react to lower doses than patients with mild reactions*" is incorrect and could be misleading. This is based on the observation by Taylor et al. (2010) that, when data were analysed on the basis of the patient's history, the threshold distribution and ED_{10} for peanut of patients with histories of more severe reactions did not differ significantly from the threshold distributions from patients with histories of less severe reactions. In addition, later studies on DBPCFCs tend to include patients with severe reactions, as well as studies conducted in subjects undergoing desensitisation treatments.

Panel consideration of comments received

Ad 75. The example was made to illustrate how food processing may affect the allergenicity of peanuts. In addition, boiled peanuts are served in Asian restaurants throughout Europe. No changes were made in the opinion on the basis of this comment.

Ad 76. The Panel notes that although there are recent studies which have not excluded patients with history of severe allergic reactions from DBPCFC, the majority of studies available have reported this practice. In addition, patients with severe reactions had lower threshold doses compared with those with mild reactions in a study conducted in 26 peanut allergic patients (Wensing et al., 2002), as mentioned in the draft opinion. The paragraph has been modified as follows: "*Few data are available on the doses that may trigger allergic reactions in patients with a history of severe allergic reactions, since they have often been excluded from oral challenge tests.*"

2.3.19. Allergy to soy

Comments received

77. A request was made to incorporate data reported by Blom et al. (2013) in the section on MEDs.

78. It was pointed out that three of the studies described in the section on MEDs (Magnolfi et al., 1996; Zeiger et al., 1999; Fiocchi et al., 2003) used Isomil® or Multisoy® infant formulas and not soy milk during challenges. It was also stated that, due to heavier processing, soy in infant formula will be closer in form to soy flour than to whole bean filtered soy milk.

Panel consideration of comments received

Ad 77. Data from the study by Blom et al. (2013) has been incorporated in the revised opinion in the section dedicated to MEDs as follows:

"In the study by Blom et al. (2013), 10 soy allergic children underwent DBPCFCs for diagnostic purposes. Children were challenged with 0.2 mg of soy protein (mucosal) and oral doses of 1.8, 3.5, 14, 70, 350, and 1 750 mg of soy protein (cumulative dose 2 190 mg). The LOAELs (expressed as discrete doses) for subjective reactions were 0.2 for one, 1.8 mg for three, 14 mg for one, 350 mg for one and 1 750 mg for four children. Only three children had objective reactions (at 0.2 mg, 350 mg and 1 750 mg, respectively)".

Ad 78. It was already stated in the draft opinion that the three studies (Magnolfi et al., 1996; Zeiger et al., 1999; Fiocchi et al., 2003) had been conducted with soy-based formula or soy-powdered formula. However, the Panel agrees that the use of the term "soy milk" thereafter in the description of the studies could lead to confusion. The draft opinion has been revised by removing the term "soy milk" in relation to those studies to avoid misunderstanding.

2.3.20. Allergy to fish

Comments received

79. It was noted that, in lines 5673-5675 of the draft opinion, a statement was made about the allergenicity of mammalian collagen, but no references were given.

80. It was pointed out that the draft opinion did not state whether the minimum reaction in Hansen and Bindslev-Jensen (1992) to 6 mg of codfish was subjective or objective, or whether the 6 mg referred to codfish or to mg of protein. It was also stated that Remington (2013) reported a cumulative MOED of 10.2 mg protein (discrete 9.15 mg protein) as the minimum objective reaction from that same study.

Panel consideration of comments received

Ad 79. Two references on the allergenicity of mammalian collagen have been added to the opinion (Fritsche et al., 2010; Land et al., 2013).

Ad 80. As explained in Section 2.2.6. of this technical report and in Section 12.2. of the revised opinion, the Panel decided to report on MEDs as in the original papers. Amounts of food were not converted into amounts of protein or vice-versa, if this information was not indicated in the paper. As indicated in the draft opinion, the study by Hansen and Bindslev-Jensen (1992) reported on mg of codfish (not on mg of protein). In addition, the symptoms reported were oropharyngeal itching (subjective) and swelling (objective). This latter information has been included in the opinion for completeness.

The text in Section 20.7 (minimum observed eliciting doses) has been modified as follows:

"Different fish species may differ with regard to the minimal eliciting dose, because of allergen heterogeneity and differences in allergen concentration in the flesh (see Section 20.3.1.1). In a DBPCFC study (Hansen and Bindslev-Jensen, 1992), the minimum dose needed to elicit a reaction (oropharyngeal itching and swelling) was 6 mg of codfish (starting dose 5 mg). Urticaria was observed after 56 mg of codfish. In a DBPCFC (Untersmayr et al., 2007), adverse reactions to codfish protein extract digested in simulated gastric fluid were studied. After digestion at pH 2.0, one subject experienced subjective symptoms after 2.11 mg protein, while after digestion at pH 3.0, one subject reported subjective symptoms after 1.11 mg, and one subject had objective signs after 2.11 mg of codfish protein.

The Panel notes that MEDs reported in DBPCFCs are 6 mg of codfish and range from 1.11 mg of codfish protein for objective symptoms to 2.11 mg for objective signs. Few data are available on the doses that may trigger allergic reactions in patients with history of severe allergic reactions, since they have often been excluded from challenge tests".

2.3.21. Allergy to crustaceans

Comments received

81. It was requested to include the study by Atkins et al. (1985) in the section on MEDs.

Panel consideration of comments received

Ad 81. The study by Atkins et al. (1985) has been included in the section on MEDs as follows:

> *"Atkins et al. (1985), in a study using open food challenges and objective signs as the outcome, reported reactions in four individuals to 25, 30 and 100 g of shrimp and 100 g of crab".*

2.3.22. Allergy to molluscs

Comments received

No specific comments were received on this section, besides those already addressed under general comments (see Sections 2.2.3, 2.2.5 and 2.2.6 of this technical report).

2.3.23. Allergy to celery

Comments received

No specific comments were received on this section, besides those already addressed under general comments (see Sections 2.2.3, 2.2.5 and 2.2.6 of this technical report).

2.3.24. Allergy to lupin

No specific comments were received on this section, besides those already addressed under general comments (see Sections 2.2.3, 2.2.5 and 2.2.6 of this technical report).

2.3.25. Allergy to sesame

Comments received

82. It was indicated that, although a DBPCFC study (Morisset et al., 2003) was described in the section on MEDs, some other studies by the same group were missed.

Panel consideration of comments received

Ad 82. The section on MEDs has been reformulated as follows:

> "*The four studies available in the literature which have reported on oral challenges in sesame allergic patients have been conducted for diagnostic purposes by the same research group in France (Kanny et al., 1996; Kolopp-Sarda et al., 1997; Morisset et al., 2003; Leduc et al., 2006).*
>
> *In one study (Morisset et al., 2003), haemodynamic modifications and respiratory symptoms were observed in 8 % and in 42 %, respectively, of the 12 positive oral challenges (SBPCFC or DBPCFC) to sesame seeds analysed. A cumulative reactive dose ≤65 mg of solid food (equivalent to 12.4 mg of sesame proteins) was found in 8 % of sesame allergic patients. The lowest eliciting dose was observed at ≤30 mg of sesame seeds (equivalent to 5.1 mg of sesame proteins). Five out of six DBPCFCs with sesame oil were positive, and two patients had an anaphylactic shock with 1 and 5 mL, respectively.*

In a subsequent study (Leduc et al., 2006), 32 patients (15 children and 17 adults) with positive history, labial test or DBPCFC to sesame seeds were challenged (DBPCFC or labial test) with either sesame seeds or sesame oil. Five were not challenged because of history of severe allergic reactions to sesame. Of the 27 patients undergoing the oral challenge, four did not react to the highest doses (965 mg and 7 g of sesame seeds). Two patients reacted with objective signs to 0.7 and 1 mL of sesame oil, respectively. One patient also reacted with objective signs to 6 mg of sesame seeds, corresponding to 1 mg of sesame protein. Systemic reactions were noted in some subjects at higher doses (965 mg, 7 g and 10 g of sesame seeds). Objective reactions to higher doses of sesame proteins were reported in the two previous studies by the same group (Kanny et al., 1996; Kolopp-Sarda et al., 1997)".

2.3.26. Allergy to mustard

Comments received

No specific comments were received on this section, besides those already addressed under general comments (see Sections 2.2.3, 2.2.5 and 2.2.6 of this technical report).

2.3.27. Adverse reactions to sulphites

Comments received

83. It was requested to considered an additional reference (Corder and Buckley, 1995) in this section, with explanation about what this reference could add to the text, or in which context.

Panel consideration of comments received

Ad 83. The Panel is unclear about what the above-mentioned reference could add to this section. No changes were made to the opinion on the basis of this comment.

2.3.28. Population thresholds calculated for some allergenic foods/ingredients

Comments received

84. See comment 55.

Panel consideration of comments received

Ad 84. See Ad 55.

EFSA wishes to thank stakeholders for their valuable comments and contributions to this Scientific Opinion.

REFERENCES

Akiyama H, Sakata K, Yoshioka Y, Murata Y, Ishihara Y, Teshima R, Sawada J and Maitani T, 2006. Profile analysis and immunoglobulin E reactivity of wheat protein hydrolysates. International Archives of Allergy and Immunology, 140, 36-42.

Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, Kruizinga AG and Taylor SL, 2014. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. Journal of Allergy and Clinical Immunology, 133, 156-164.

Atkins FM, Steinberg SS and Metcalfe DD, 1985. Evaluation of immediate adverse reactions to foods in adult patients. II. A detailed analysis of reaction patterns during oral food challenge. Journal of Allergy and Clinical Immunology, 75, 356-363.

Bakos N, Scholl I, Szalai K, Kundi M, Untersmayr E and Jensen-Jarolim E, 2006. Risk assessment in elderly for sensitization to food and respiratory allergens. Immunology Letters, 107, 15-21.

Blom WM, Vlieg-Boerstra BJ, Kruizinga AG, van der Heide S, Houben GF and Dubois AE, 2013. Threshold dose distributions for 5 major allergenic foods in children. Journal of Allergy and Clinical Immunology, 131, 172-179.

Bonds RS, Midoro-Horiuti T and Goldblum R, 2008. A structural basis for food allergy: the role of cross-reactivity. Current Opinion in Allergy and Clinical Immunology, 8, 82-86.

Brown SJ, Asai Y, Cordell HJ, Campbell LE, Zhao Y, Liao H, Northstone K, Henderson J, Alizadehfar R, Ben-Shoshan M, Morgan K, Roberts G, Masthoff LJ, Pasmans SG, van den Akker PC, Wijmenga C, Hourihane JO, Palmer CN, Lack G, Clarke A, Hull PR, Irvine AD and McLean WH, 2011. Loss-of-function variants in the filaggrin gene are a significant risk factor for peanut allergy. Journal of Allergy and Clinical Immunology, 127, 661-667.

Bublin M, Eiwegger T and Breiteneder H, 2014. Do lipids influence the allergic sensitization process? Journal of Allergy and Clinical Immunology, 134, 521-529.

Burks AW, Jones SM, Boyce JA, Sicherer SH, Wood RA, Assa'ad A and Sampson HA, 2011. NIAID-sponsored 2010 guidelines for managing food allergy: applications in the pediatric population. Pediatrics, 128, 955-965.

Caballero T, Pascual C, GarcÍA-Ara MC, Ojeda JA and MartÍN-Esteban M, 1997. IgE crossreactivity between mugwort pollen (Artemisia vulgaris) and hazelnut (Abellana nux) in sera from patients with sensitivity to both extracts. Clinical and Experimental Allergy, 27, 1203-1211.

Carter CM, Urbanowicz M, Hemsley R, Mantilla L, Strobel S, Graham PJ and Taylor E, 1993. Effects of a few food diet in attention deficit disorder. Archives of Disease in Childhood, 69, 564-568.

Commins SP, Satinover SM, Hosen J, Mozena J, Borish L, Lewis BD, Woodfolk JA and Platts-Mills TA, 2009. Delayed anaphylaxis, angioedema, or urticaria after consumption of red meat in patients with IgE antibodies specific for galactose-alpha-1,3-galactose. Journal of Allergy and Clinical Immunology, 123, 426-433.

Corder EH and Buckley CE, 3rd, 1995. Aspirin, salicylate, sulfite and tartrazine induced bronchoconstriction. Safe doses and case definition in epidemiological studies. Journal of Clinical Epidemiology, 48, 1269-1275.

Crevel RW, Kerkhoff MA and Koning MM, 2000. Allergenicity of refined vegetable oils. Food and Chemical Toxicology, 38, 385-393.

Davis PJ and Williams SC, 1998. Protein modification by thermal processing. Allergy, 53, 102-105.

de Silva D, Geromi M, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Cardona V, Dubois AE, Halken S, Host A, Poulsen LK, Van Ree R, Vlieg-Boerstra BJ, Agache I, Sheikh A and Group EFAAG, 2014. Acute and long-term management of food allergy: systematic review. Allergy, 69, 159-167.

Defernez M, Rigby NM, Johnson PE, Dainty J, Sperrin M, Mackie AR and Mills C, 2013. Management of food allergens: from threshold doses to analysis in foods - Food Standards Agency Project T07062 - Final Report.

Denery-Papini S, Bodinier M, Larre C, Brossard C, Pineau F, Triballeau S, Pietri M, Battais F, Mothes T, Paty E and Moneret-Vautrin DA, 2012. Allergy to deamidated gluten in patients tolerant to wheat: specific epitopes linked to deamidation. Allergy, 67, 1023-1032.

Don C, Hallmayr-Jech E, Rogers A and Koehler P, 2014. AACCI Approved Methods Technical Committee report: collaborative study on the immunochemical quantitation of intact gluten in rice flour and rice-based products using G12 sandwich ELISA. Cereal Foods World, 59, 187-193.

EFSA (European Food Safety Authority), 2004. Opinion of the Scientific Panel on Dietetic products, Nutrition and Allergies (NDA) on a request from the Commission relating to the evaluation of allergenic foods for labelling purposes. The EFSA Journal 2004, 32, 1-197.

EFSA (European Food Safety Authority), 2006a. Opinion of the Scientific Panel on Dietetic products, Nutrition and Allergies (NDA) related to the evaluation of molluscs for labelling purposes. The EFSA Journal 2006, 327, 1-11.

EFSA (European Food Safety Authority), 2006b. Opinion of the Scientific Panel on Dietetic products, Nutrition and Allergies (NDA) related to the evaluation of lupin for labelling purposes. The EFSA Journal 2006, 302, 1-11.

EFSA NDA Panel (EFSA Panel on Dietetic Products, Nutrition and Allergies), 2014. Scientific Opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. EFSA Journal 2014;12(11):3894, 202 pp. doi:10.2903/j.efsa.2014.3894

Eller E, Hansen TK and Bindslev-Jensen C, 2012. Clinical thresholds to egg, hazelnut, milk and peanut: results from a single-center study using standardized challenges. Annals of Allergy, Asthma, and Immunology, 108, 332-336.

Estrada-Girón Y, Swanson BG and Barbosa-Cánovas GV, 2005. Advances in the use of high hydrostatic pressure for processing cereal grains and legumes. Trends in Food Science & Technology, 16, 194-203.

Filipiak-Pittroff B, Schnopp C, Berdel D, Naumann A, Sedlmeier S, Onken A, Rodriguez E, Folster-Holst R, Baurecht H, Ollert M, Ring J, Cramer C, von Berg A, Bauer CP, Herbarth O, Lehmann I, Schaaf B, Koletzko S, Wichmann HE, Heinrich J, Weidinger S and groups GaLs, 2011. Predictive value of food sensitization and filaggrin mutations in children with eczema. Journal of Allergy and Clinical Immunology, 128, 1235-1241 e1235.

Fiocchi A, Travaini M, D'Auria E, Banderali G, Bernardo L and Riva E, 2003. Tolerance to a rice hydrolysate formula in children allergic to cow's milk and soy. Clinical and Experimental Allergy, 33, 1576-1580.

Flinterman AE, Hoekstra MO, Meijer Y, van Ree R, Akkerdaas JH, Bruijnzeel-Koomen CA, Knulst AC and Pasmans SG, 2006. Clinical reactivity to hazelnut in children: association with sensitization to birch pollen or nuts? Journal of Allergy and Clinical Immunology, 118, 1186-1189.

Fritsche PJ, Helbling A and Ballmer-Weber BK, 2010. Vaccine hypersensitivity--update and overview. Swiss Medical Weekly, 140, 238-246.

Grimshaw KE, King RM, Nordlee JA, Hefle SL, Warner JO and Hourihane JO, 2003. Presentation of allergen in different food preparations affects the nature of the allergic reaction--a case series. Clinical and Experimental Allergy, 33, 1581-1585.

Hansen TK and Bindslev-Jensen C, 1992. Codfish allergy in adults. Identification and diagnosis. Allergy, 47, 610-617.

Hauser M, Roulias A, Ferreira F and Egger M, 2010. Panallergens and their impact on the allergic patient. Allergy, Asthma & Clinical Immunology, 6, 1.

Hirschwehr R, Valenta R, Ebner C, Ferreira F, Sperr WR, Valent P, Rohac M, Rumpold H, Scheiner O and Kraft D, 1992. Identification of common allergenic structures in hazel pollen and hazelnuts: a possible explanation for sensitivity to hazelnuts in patients allergic to tree pollen. Journal of Allergy and Clinical Immunology, 90, 927-936.

Hompes S, Kohli A, Nemat K, Scherer K, Lange L, Rueff F, Rietschel E, Reese T, Szepfalusi Z, Schwerk N, Beyer K, Hawranek T, Niggemann B and Worm M, 2011. Provoking allergens and

treatment of anaphylaxis in children and adolescents--data from the anaphylaxis registry of German-speaking countries. Pediatric Allergy and Immunology, 22, 568-574.

Huang H-W, Hsu C-P, Yang BB and Wang C-Y, 2014. Potential utility of high-pressure processing to address the risk of food allergen concerns. Comprehensive Reviews in Food Science and Food Safety, 13, 78-90.

Immer U and Haas Lauterbach S, 2010. Gluten detection in molecular biological and immunological techniques and applications for food chemists. In: Eds Popping B, Diaz-Amigo C and Hoenicke K. John Wiley & Sons, Inc, 359-375.

Isolauri E, Tahvanainen A, Peltola T and Arvola T, 1999. Breast-feeding of allergic infants. Journal of Pediatrics, 134, 27-32.

Johnson PE, Rigby NM, Dainty JR, Mackie AR, Immer UU, Rogers A, Titchener P, Shoji M, Ryan A, Mata L, Brown H, Holzhauser T, Dumont V, Wykes JA, Walker M, Griffin J, White J, Taylor G, Popping B, Crevel R, Miguel S, Lutter P, Gaskin F, Koerner TB, Clarke D, Sherlock R, Flanagan A, Chan CH and Mills EN, 2014. A multi-laboratory evaluation of a clinically-validated incurred quality control material for analysis of allergens in food. Food Chem, 148, 30-36.

Kanny G, De Hauteclocque C and Moneret-Vautrin DA, 1996. Sesame seed and sesame seed oil contain masked allergens of growing importance. Allergy, 51, 952-957.

Kennedy JL, Stallings AP, Platts-Mills TA, Oliveira WM, Workman L, James HR, Tripathi A, Lane CJ, Matos L, Heymann PW and Commins SP, 2013. Galactose-alpha-1,3-galactose and delayed anaphylaxis, angioedema, and urticaria in children. Pediatrics, 131, e1545-1552.

Kleber N, Maier S and Hinrichs J, 2007. Antigenic response of bovine β-lactoglobulin influenced by ultra-high pressure treatment and temperature. Innovative Food Science & Emerging Technologies, 8, 39-45.

Koletzko S, Niggemann B, Arato A, Dias JA, Heuschkel R, Husby S, Mearin ML, Papadopoulou A, Ruemmele FM, Staiano A, Schappi MG, Vandenplas Y and European Society of Pediatric Gastroenterology H, and Nutrition., 2012. Diagnostic approach and management of cow's-milk protein allergy in infants and children: ESPGHAN GI Committee practical guidelines. Journal of Pediatric Gastroenterology and Nutrition, 55, 221-229.

Kolopp-Sarda MN, Moneret-Vautrin DA, Gobert B, Kanny G, Brodschii M, Bene MC and Faure GC, 1997. Specific humoral immune responses in 12 cases of food sensitization to sesame seed. Clinical and Experimental Allergy, 27, 1285-1291.

Land MH, Piehl MD and Burks AW, 2013. Near fatal anaphylaxis from orally administered gelatin capsule. Journal of Allergy and Clinical Immunology: In Practice, 1, 99-100.

Leduc V, Moneret-Vautrin DA, Tzen JT, Morisset M, Guerin L and Kanny G, 2006. Identification of oleosins as major allergens in sesame seed allergic patients. Allergy, 61, 349-356.

Machtinger S and Moss R, 1986. Cow's milk allergy in breast-fed infants: the role of allergen and maternal secretory IgA antibody. Journal of Allergy and Clinical Immunology, 77, 341-347.

Magnolfi CF, Zani G, Lacava L, Patria MF and Bardare M, 1996. Soy allergy in atopic children. Annals of Allergy, Asthma, and Immunology, 77, 197-201.

Masthoff LJ, Mattsson L, Zuidmeer-Jongejan L, Lidholm J, Andersson K, Akkerdaas JH, Versteeg SA, Garino C, Meijer Y, Kentie P, Versluis A, den Hartog Jager CF, Bruijnzeel-Koomen CA, Knulst AC, van Ree R, van Hoffen E and Pasmans SG, 2013. Sensitization to Cor a 9 and Cor a 14 is highly specific for a hazelnut allergy with objective symptoms in Dutch children and adults. Journal of Allergy and Clinical Immunology, 132, 393-399.

McCann D, Barrett A, Cooper A, Crumpler D, Dalen L, Grimshaw K, Kitchin E, Lok K, Porteous L, Prince E, Sonuga-Barke E, Warner JO and Stevenson J, 2007. Food additives and hyperactive

behaviour in 3-year-old and 8/9-year-old children in the community: a randomised, double-blinded, placebo-controlled trial. Lancet, 370, 1560-1567.

Meglio P, Giampietro PG, Carello R, Gabriele I, Avitabile S and Galli E, 2013. Oral food desensitization in children with IgE-mediated hen's egg allergy: a new protocol with raw hen's egg. Pediatric Allergy and Immunology, 24, 75-83.

Mills EN and Mackie AR, 2008. The impact of processing on allergenicity of food. Current Opinion in Allergy and Clinical Immunology, 8, 249-253.

Mills EN, Sancho AI, Rigby NM, Jenkins JA and Mackie AR, 2009. Impact of food processing on the structural and allergenic properties of food allergens. Molecular Nutrition and Food Research, 53, 963-969.

Morisset M, Moneret-Vautrin DA, Kanny G, Guenard L, Beaudouin E, Flabbee J and Hatahet R, 2003. Thresholds of clinical reactivity to milk, egg, peanut and sesame in immunoglobulin E-dependent allergies: evaluation by double-blind or single-blind placebo-controlled oral challenges. Clinical and Experimental Allergy, 33, 1046-1051.

Moron B, Cebolla A, Manyani H, Alvarez-Maqueda M, Megias M, Thomas Mdel C, Lopez MC and Sousa C, 2008. Sensitive detection of cereal fractions that are toxic to celiac disease patients by using monoclonal antibodies to a main immunogenic wheat peptide. American Journal of Clinical Nutrition, 87, 405-414.

Muraro A, Halken S, Arshad SH, Beyer K, Dubois AE, Du Toit G, Eigenmann PA, Grimshaw KE, Hoest A, Lack G, O'Mahony L, Papadopoulos NG, Panesar S, Prescott S, Roberts G, de Silva D, Venter C, Verhasselt V, Akdis AC, Sheikh A and Group EFAAG, 2014a. EAACI food allergy and anaphylaxis guidelines. Primary prevention of food allergy. Allergy, 69, 590-601.

Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Beyer K, Bindslev-Jensen C, Cardona V, Dubois A, duToit G, Eigenmann P, Fernandez Rivas M, Halken S, Hickstein L, Host A, Knol E, Lack G, Marchisotto MJ, Niggemann B, Nwaru BI, Papadopoulos NG, Poulsen LK, Santos AF, Skypala I, Schoepfer A, Van Ree R, Venter C, Worm M, Vlieg-Boerstra B, Panesar S, de Silva D, Soares-Weiser K, Sheikh A, Ballmer-Weber BK, Nilsson C, de Jong NW, Akdis CA and Group EFAAG, 2014b. EAACI food allergy and anaphylaxis guidelines: diagnosis and management of food allergy. Allergy, 69, 1008-1025.

Nordlee JA, Remington BC, Ballmer-Weber BK, Lehrer SB, Baumert JL and Taylor SL, 2013. Threshold dose for shrimp: a risk characterization based on objective reactions in clinical studies. Journal of Allergy and Clinical Immunology, 131, AB88.

Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, Dubois AE, Halken S, Hoffmann-Sommergruber K, Poulsen LK, Roberts G, Van Ree R, Vlieg-Boerstra BJ, Sheikh A and Group EFAAG, 2014a. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy, 69, 62-75.

Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A and Group EFAAG, 2014b. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy, 69, 992-1007.

Patriarca G, Buonomo A, Roncallo C, Del Ninno M, Pollastrini E, Milani A, De Pasquale T, Gasbarrini G, Schiavino D and Nucera E, 2002. Oral desensitisation in cow milk allergy: immunological findings. International Journal of Immunopathology and Pharmacology, 15, 53-58.

Pellegrino L and Tirelli A, 2000. A sensitive HPLC method to detect hen's egg white lysozyme in milk and dairy products. International Dairy Journal, 10, 435-442.

Peñas E, Gomez R, Frias J, Baeza ML and Vidal-Valverde C, 2011. High hydrostatic pressure effects on immunoreactivity and nutritional quality of soybean products. Food Chemistry, 125, 423-429.

Poms RE, Klein CL and Anklam E, 2004a. Methods for allergen analysis in food: a review. Food Additives and Contaminants, 21, 1-31.

Remington B, 2013. Risk Assessment of Trace and Undeclared Allergens in Processed Foods. Dissertations & Theses in Food Science and Technology, Paper 32.

Sampson HA, Gerth van Wijk R, Bindslev-Jensen C, Sicherer S, Teuber SS, Burks AW, Dubois AE, Beyer K, Eigenmann PA, Spergel JM, Werfel T and Chinchilli VM, 2012. Standardizing double-blind, placebo-controlled oral food challenges: American Academy of Allergy, Asthma & Immunology-European Academy of Allergy and Clinical Immunology PRACTALL consensus report. Journal of Allergy and Clinical Immunology, 130, 1260-1274.

Schneider N, Weigel I, Werkmeister K and Pischetsrieder M, 2010. Development and validation of an enzyme-linked immunosorbent assay (ELISA) for quantification of lysozyme in cheese. Journal of Agricultural and Food Chemistry, 58, 76-81.

Sletten G, Van Do T, Lindvik H, Egaas E and Florvaag E, 2010. Effects of industrial processing on the immunogenicity of commonly ingested fish species. International Archives of Allergy and Immunology, 151, 223-236.

Soares-Weiser K, Takwoingi Y, Panesar SS, Muraro A, Werfel T, Hoffmann-Sommergruber K, Roberts G, Halken S, Poulsen L, van Ree R, Vlieg-Boerstra BJ, Sheikh A and Group EFAAG, 2014. The diagnosis of food allergy: a systematic review and meta-analysis. Allergy, 69, 76-86.

Sykes M, Anderson D and Parmar B, 2012. Normalisation of data from allergens proficiency tests. Analytical and Bioanalytical Chemistry, 403, 3069-3076.

Taylor SL, Moneret-Vautrin DA, Crevel RW, Sheffield D, Morisset M, Dumont P, Remington BC and Baumert JL, 2010. Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. Food and Chemical Toxicology, 48, 814-819.

Taylor SL, Baumert JL, Kruizinga AG, Remington BC, Crevel RW, Brooke-Taylor S, Allen KJ, Allergen Bureau of A, New Z and Houben G, 2014. Establishment of reference doses for residues of allergenic foods: report of the VITAL Expert Panel. Food and Chemical Toxicology, 63, 9-17.

Tolin S, Pasini G, Curioni A, Arrigoni G, Masi A, Mainente F and Simonato B, 2012. Mass spectrometry detection of egg proteins in red wines treated with egg white. Food Control, 23, 87-94.

University of Portsmouth, 2013. Literature searches and reviews related to the prevalence of food allergy in Europe. Project developed as part of procurement project CFT/EFSA/NUTRI/2012/02. 343 pp.

Untersmayr E, Vestergaard H, Malling HJ, Jensen LB, Platzer MH, Boltz-Nitulescu G, Scheiner O, Skov PS, Jensen-Jarolim E and Poulsen LK, 2007. Incomplete digestion of codfish represents a risk factor for anaphylaxis in patients with allergy. Journal of Allergy and Clinical Immunology, 119, 711-717.

van den Oord RA and Sheikh A, 2009. Filaggrin gene defects and risk of developing allergic sensitisation and allergic disorders: systematic review and meta-analysis. British Medical Journal (Clinical Research Ed.), 339, b2433.

Venkataraman D, Soto-Ramirez N, Kurukulaaratchy RJ, Holloway JW, Karmaus W, Ewart SL, Arshad SH and Erlewyn-Lajeunesse M, 2014. Filaggrin loss-of-function mutations are associated with food allergy in childhood and adolescence. Journal of Allergy and Clinical Immunology.

Vieths S, Scheurer S and Ballmer-Weber B, 2002. Current understanding of cross-reactivity of food allergens and pollen. Annals of the New York Academy of Sciences, 964, 47-68.

Wensing M, Penninks AH, Hefle SL, Koppelman SJ, Bruijnzeel-Koomen CAFM and Knulst AC, 2002. The distribution of individual threshold doses eliciting allergic reactions in a population with peanut allergy. Journal of Allergy and Clinical Immunology, 110, 915-920.

Zeiger RS, Sampson HA, Bock SA, Burks AW, Jr., Harden K, Noone S, Martin D, Leung S and Wilson G, 1999. Soy allergy in infants and children with IgE-associated cow's milk allergy. Journal of Pediatrics, 134, 614-622.

APPENDICES

Appendix A. Explanatory text published in relation to the public consultation on the draft scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes

EFSA has launched an open consultation on the draft scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. This document updates previous EFSA opinions relative to food ingredients or substances with known allergenic potential listed in Annex IIIa of 2003/89/EC, as amended. It includes information on the prevalence of food allergy in unselected populations, on proteins identified as food allergens, on cross-reactivities, on the effects of food processing on allergenicity of foods and ingredients, on methods for the detection of allergens and allergenic foods, on doses observed to trigger adverse reactions in sensitive individuals, and on the approaches which have been used to derive individual and population thresholds for selected allergenic foods.

In line with EFSA's policy on openness and transparency and in order for EFSA to receive comments from the scientific community and stakeholders, EFSA has launched a public consultation on the draft document developed by the NDA Panel of EFSA.

Interested parties are invited to submit written comments by 8 August 2014. Please use exclusively the electronic template provided with the documents to submit comments and refer to the line and page numbers. Please note that comments submitted by e-mail or by post cannot be taken into account and that a submission will not be considered if it is:

- submitted after the deadline set out in the call
- presented in any form other than what is provided for in the instructions and template
- not related to the contents of the document
- contains complaints against institutions, personal accusations, irrelevant or offensive statements or material
- is related to policy or risk management aspects, which is out of the scope of EFSA's activity.

EFSA will assess all comments from interested parties which are submitted in line with the criteria above. The comments will be further considered by the relevant EFSA Panel and taken into consideration if found to be relevant.

All comments submitted will be published. Comments submitted by individuals in a personal capacity will be presented anonymously. Comments submitted formally on behalf of an organisation will appear with the name of the organisation.

Appendix B. Full list of comments submitted by means of electronic form on the EFSA website

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
1. Introduction	AFDIAG	It seems that fundamentally, the question is : what kind of food, regarding its content, a consumer can reasonably wait for when buying its food? Nowadays, in UE, all ingredients that had been voluntary incorporated in the recipe must appear on the ingredients list. 14 substances are listed in Annex III a of former regulation that become Annex II of 2011/1169. They are said to be allergenic (that mean the main dangerous in food, knowing that a lot more ingredients are also know to provoke allergic reactions). They must be labelled even if they are only flavour supports and will be emphasized on ingredient lists as soon as December 13th 2014. But controls show that substances not listed in the ingredients lists might be present due to process error, label error, cross contamination during process or fraud. IFSA demand for EFSA advice deals not on voluntary included ingredients that regulation deals with, but on those unintended ingredients. Two categories might have been look at but only the first seems to had been considered by the panel : standard food : food manufacturers had developed the habit of may contain labels without any regulation. The EFSA scientific opinion is awaited as a basis for definition of "standard food" as we've got a safe food in bacteriological field; food with allegation : what about "free from" food ? The market is increasing even if, apart for gluten free, there is no regulation for that. Consumers note that threshold and analytical method for gluten drove to an explosion of allegation even on naturally free from gluten food that mustn't wear this mention. The plus value is real for industry as shown by some marketing studies. To day, a consumer buying an egg free food don't know if it contents less egg than a standard food with no egg on its recipe. May contain (precautionary label) : in France, C.N.A. (conseil national de l'alimentation) which aggregate stake holders of the all food chain, didn't find consensus for may contain label : consumers refuse them, food manuf acturers want them. EFSA scientific opinion don't give any answer. consumers : for a consumer, it is impossible to know if a food with a may contain label really contains or not the ingredient, and even less how much is potentially on it. Several studies shown that consumers don't use those mentions to decide to buy a product. EFSA draft miss to mention studies about accident linked to may contain food consumption if they exist. Controls bodies : without quantitative threshold, controls drive to food recall as soon as qualitative test is positive (that means at the sensitivity of the methods). But a 20 ppm or 1000 ppm content don't represent the same risk for sensitive consumer.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Food manufacturer : allergen risk analyse must be part of HACCP. Official thresholds might help, but the manufacturer can choose its own threshold. Ther is no naturel link between HACCP and label (look at bacteriological, chemical or physical hazards). Labs : when conceiving a new recipe or a new process, food manufacture r must validate control methods (matrix effect) to be able afterward to control production. Dosage kits which are said to dose an ingredient generally only dose part of it (example : cor 8 for hazelnut) and can't be said to detect all hazelnut. The same for yolk or white part of the egg. EFSA opinion might include all those points.
1. Introduction	Anaphylaxis Campaign	p4 Lines 119 - 130 - EFSA concludes, that "current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer". This conclusion is based on the following: a. "Most clinicians exclude from the challenge studies those patients having the most severe reactions" (Row 126) b. "Reliability of these thresholds has not been tested prospectively in real life conditions yet" (row 127) c. Patients are not aware of their own individual threshold levels (rows 120-130) EFSA states that current data do not allow for the determination of thresholds, which will mean that the regulation of PAL is highly unlikely to be addressed. The uncertainty and dissatisfaction that currently exists with the current use of PAL is therefore unlikely to change in the near future and allergic consumers will continue to be unable to judge from looking at a food label whether: a) A product bearing PAL does or does not carry a genuine risk of cross contamination b) The absence of PAL does or does not indicate a "safe" product. Consequently, food allergic consumers will continue to be unable to make an informed, safe evidence-based assessment and choice when buying food. "Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer" EFSA's statement regarding "safe thresholds " does not take into consideration conclusions drawn from discussions at various international stakeholder meetings on this topic (e.g. Europrevall/ FSA meeting in Vienna 2012 and the ILSI meeting in Reading 2013). Discussions at these meetings concluded that 100% safety for all allergic consumers from any kind of allergic reaction is neither achievable nor realistic. A certain level of risk of allergic reaction will always be present for the most sensitive allergic consumers, BUT the establishment of thresholds as a basi s for food labelling should help to protect allergic consumers from severe reactions. As the term "adverse reactions" is not defined, it is not surprising that "current clinical, epidemiological and experimental data" demonstrating threshold levels below which no reactions occur, are not available. The protection of every allergic consumer from every allergic reaction is not feasible, nor is it supported by patient stakeholder groups. Undertaking to determine zero risk for all allergic consumers would mean that threshold levels are

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		unlikely ever to be agreed. The EFSA Opinion correctly states that "dietary avoidance of specific allergenic foods … is the mainstay of management in IgE-mediated and non-IgE-mediated food allergy"(Rows 54-56), but does not take food labelling and allergen information into consideration. Allergic consumers are only able to avoid their specific food allergen if the allergen information they receive is accurate, clear, reliable and consistent. . There are currently no univ ersally agreed standards by which PAL is applied that would demonstrate transparency and confidence in its presence or absence. The allergic consumer is therefore currently unable, effectively and reliably, to avoid specific allergenic foods due to the shortcomings of PAL. Allergic consumers/ patient groups, clinicians and National and International allergy organisations such as EAACI in the EU and WAO globally, see the need for mandatory standards on allergen and allergy-risk management based on an agreed and consistent method of allergy risk assessment.
1. Introduction	Anaphylaxis Campaign	p4 Line127 - 4. "Reliability of these thresholds has not been tested prospectively in real life conditions yet" This statement is also correct at the current point in time, however there are several research projects currently being undertaken that should provide data that will inform this issue in the near future. These include the one-dose challenges that are being undertaken as part of the iFAAM project in Europe and from FARRP in the USA. Data on extrinsic factors such as stress and physical activity and their influence on individual threshold levels will also be available from the ongoing TRACE study funded by the Food Standards Agency (FSA) in the UK. . Although these data are not currently available they are likely to provide important evidence in the near future and should therefore be taken into account when considering the issue of the establishment of thresholds for specific allergenic foods. The data are likely to be available within the next few years and certainly before the next EFSA evaluation in 10 years time.
1. Introduction	Anaphylaxis Campaign	p4 Lines 129 - 130 - 5. Patients are not aware of their own individual threshold levels (rows 120-130) It is correct that most patients do not know their individual thresholds. Ongoing research such as the FSA / UK TRACE study and the EU iFAAM project are also seeking to demonstrate that that reactions and individual threshold levels can vary under certain circumstances in the same individual. The determination of thresholds/ reference doses would assist clinicians in undertaking more effective testing in their patients and enable them to offer clearer and more helpful dietary advice. In addition to helping to minimise risk, the establishment of standards for Risk Assessment defined by agreed threshold levels would improve the Quality of Life (QoL) of food allergic consumers by: • increasing informed consumer choice when shopping for food • generating greater trust in food labels • Improving the transparency and consistency of food labelling

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• minimising anxiety when food shopping • allo wing greater consistency in allergen management throughout the food industry • enabling better communication to healthcare providers and consumers on the meaning of PAL
1. Introduction	EuroCommerce	Dear Sir or Madam, Thank you for giving us the opportunity to comment on the public consultation on the draft scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. Since 2003 European legislation has covered provisions on the labelling of allergens. These provisions cover the deliberate use of an allergen directly or within an ingredient. In addition, Regulation 178/2002 requires that all food placed in the market is safe. Retailers take their responsibility to place safe food in the market very seriously; one aspect of making sure the food is safe is understanding the potential risk of a foodstuff being cross contaminated with one of the 14 common allergens. Retailers have thorough risk assessments through which they establish the possible risk of contamination, how the risks can be mitigated and whether there is a need to alert the allergenic consumer of the possible risk through a statement on the label. Over the years the risk assessment proc ess has been strengthened; however retailers believe that further strengthening is limited by the lack of threshold concentrations for each one of the common allergens. A harmonious way of determining risk is to define thresholds that would provide an acceptable level of protection for the majority of at-risk consumers and limit the labelling of risk, so increasing consumers' confidence in the risk labelling. Based on the mandate given to EFSA, we understood that this would be one of the aspects covered in the draft EFSA opinion; however having read the draft opinion we believe EFSA has deviated from the mandate. The draft opinion would suggest that EFSA has instead looked at whether a level can be set for each allergen below which no allergenic person would react. Having waited for the publication of the opinion for 3 years, we are concerned that this draft opinion will prevent the development of consistent public policy on allergen cross contamination, as envisaged under Article 36.3 (a) of Regulat ion 1169/2011 on the food information to consumers. This will ultimately prevent the development of better informed and consistent risk assessments. Conclusion: EFSA should/must reflect back on the mandate given to them by the Food Safety Authority of Ireland (FSAI) and revisit the opinion
1. Introduction	European Federation of Allergy and Airways Diseases	The motivations behind the request of the draft opinion were extremely positive as it was thought that it would have helped to assess the exact number of allergy cases in Europe, however, due to the way the opinion is drafted such opportunity is missed . The experts are not using the latest updated data (e.g. the results of the EUROPERAVALL Project on food allergy

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
	Patients' Associations (EFA)	held within the FP6 framework) and some studies mentioned are very old and outdated. The opinion does not propose anything really new, as EFSA experts are not suggesting to change the list of the existing 14 allergens (by adding new ones and/or deleting others according to recent research) nor establishing thresholds/reference doses. It does not take into account what people with food allergy are requesting, does not focus on the quality of life aspects and does not result in policy change regarding precautionary labelling.
1. Introduction	Faculty of Medicine, NANCY France - Consultant in the Allergy dDpartment Hospital Center EPINAL Fra	This is an outstanding report on food allergens and food allergies, being a significant contribution to the dissemination of the present knowledge. I have scarce comments that may improve the final text. All of these comments are related to the clinical presentation of food allergies that is clearly insufficient
1. Introduction	Familles Rurales	EFSA had partially updated its 2004 report. But this draft missed some of the recent publications as Europrevall (European funded project). Some very old studies are still used and might have been updated (line 4836 - Olszewski et al. 1998 for crude peanut oil). It seems that fundamentally, the question is: what kind of food, regarding to its content, a consumer can reasonably wait for when buying its food? Nowadays, in UE, all ingredients that had been voluntary incorporated in the recipe must appear on the ingredients list. Especially, 14 substances or products causing allergies or intolerances, listed in Annex II of 2011/1169 regulation must be labelled even if they are only flavour supports and will be emphasized in ingredient lists as soon as December 13th 2014. But controls show that substances not listed might be present due to process error, label error, cross contamination during process or fraud. IFSA demand for EFSA advice deals not on voluntary included ingredients that regulation deals with, but on those unintended ingredients. Two categories might have been looked at but only the first seems to have been considered by the panel: - Standard food: food manufacturers have developed the habit of may contain labels without any regulation. The EFSA scientific opinion is awaited as a basis for definition of "standard food" as we've got a safe food in bacteriological or residue fields; - Food with allegation: what about "free from" food? The market is increasing even if, apart from gluten free, no regulation exists. Consumers note that validation of threshold and analytical method for gluten have driven to an explosion of allegation even on naturally free from gluten food that mustn't wear this mention. The plus value is real for industry as shown by some marketing studies. Today, a consumer buying food labelled "egg free", don't know if it contains less egg than a standard food with no egg in its recipe. May contain (precautionary label): in France, C.N.A. (Conseil National de l'Alimentation) which aggregate stakeholders of

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		the all food chain, didn't find consensus for may contain label : consumers refuse them, food manufacturers want them. EFSA scientific opinion don't give any answer. - Consumers: for consumers, it is impossible to know if a food with a may contain label really contains or not the ingredient, and even less how much is potentially in it. Several studies showed that consumers don't use those mentions to decide to buy a product. EFSA draft misses to mention studies about accident linked to may contain food consumption, if they exist. - Control bodies: without quantitative threshold, controls drive to food recall as soon as qualitative test is positive (that means at the sensitivity of the methods). But a 20 ppm or 1000 ppm content don't represent the same risk for a sensitive consumer. - Food manufacturers: allergen risk analysis must be part of HACCP. Official thresholds might help, but manufacturers can choose their own threshold. Anyway, this should not drive to labelling just like in case of bacteriological risk management. For example, nowhere, food is labelled hepatitis E virus free! - Labs: when conceiving a new recipe or a new process, food manufacturer must validate control methods (matrix effect) to be able afterwards to control production. Dosage kits usually dose a characteristic molecule of the ingredient which may not be the or the only allergenic one. As manufacturers use more and more only extracts of ingredients, those kits can't conclude at the absence of the ingredient (ex: cor 8 for hazelnut).The same for yolk or white part of the egg.
1. Introduction	FEDIOL	FEDIOL is the European federation representing the interests of the vegetable oil and protein meal industry. FEDIOL members are 12 national associations of oilseed crushers and refiners and 5 associated members, extending the scope of FEDIOL to 17 Member States. Directly and indirectly, FEDIOL covers about 150 processing sites that crush oilseeds and/or refine crude vegetable oils. These plants belong to around 35 companies. It is estimated that over 80% of the EU crushing and refining activity is covered by the FEDIOL membership structure. FEDIOL welcomes the opportunity to contribute to the current consultation. Allergenic foods and their labeling is an important issue which needs to be based on risk analysis, validated methodologies, sound scientific developments, as well as data and studies using strict quality requirements. FEDIOL welcomes the draft scientific opinion on the evaluation of allergenic foods and food ingredients for labeling purposes. Overall it is felt that it leaves significant ro om of interpretation on a number of issues and does not necessarily give precise conclusions. Whilst FEDIOL acknowledges the complexity of the issue and the mandate given to EFSA, FEDIOL considers that the value of the Opinion could be significantly enhanced by closer alignment with the mandate from the FSAI. Specifically, it was hoped that the EFSA draft opinion would form the basis of robust quantitative risk assessment, which could permit leading improvement in the way allergens are managed and thereby significantly improve food safety for those at risk from allergenic foods. Additionally, this would enable the final Opinion to better serve the EU policy objectives e.g. as expressed in Regulation 1169/2011.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		FEDIOL has outlined the following arguments which are also detailed in the specific sections below: • Clear criteria for considering a food/food group as allergenic are needed (section 6). • Processing does have effects on allergenicity and should be exemplified (section 10). • Setting clear cr iteria and guidance including on quality criteria for inclusion and exclusion of studies for consideration is crucial (section 12). • Details should be provided on risk from exposure to tree nuts and their derived products, given the exemptions also granted so far (section 17). • As highlighted under section 12, clear inclusion and exclusion criteria for considering a study or not are crucial, as several known studies have not been considered in section 18. • The exemption granted for N/RBD soybean oil by EFSA is essential to mention for clarity and content (section 19).
1. Introduction	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
1. Introduction	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define “high temperature” for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – “Almonds are not nuts…” a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo ‘DBPCFC’ not ‘DBPCFG’ • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
1. Introduction	FoodDrinkEurope	Introduction (lines 616-626) A recent meta-analysis on the epidemiology of food allergy in Europe by Nwaru et al* was published in January 2014, which

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		illustrates the strength of a systematic analysis, leading to new insights. *Nwaru BI(1), Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A; the EAACI Food Allergy and Anaphylaxis Guidelines Group.Allergy. 2014 May 10. doi: 10.1111/all.12423. [Epub ahead of print] Prevalence of common food allergies in Europe: a systematic review and meta-analysis.
1. Introduction	FoodDrinkEurope	The Food Safety Authority of Ireland set out very clearly three broad areas that they wish EFSA to consider (lines 604-607): • The prevalence of each allergy in the European Union. • Recommendations for threshold concentrations of each allergen in food that would provide an acceptable level of protection for at-risk consumers; • The suitability, or otherwise, of qualitative and quantitative DNA-based tests (PCR) for the detection and quantification of food allergens in comparison with immunological (e.g. ELISA) or other methods." (lines 608-613) The mandate clearly has three areas of focus. Prevalence and suitability of analytical methodology are self-explanatory, but the wording around thresholds contains a degree of ambiguity. It involves the consideration of "acceptable risk", which is a risk management tool. Risk management and risk assessment are split responsibilities according to the risk analysis process. Decisions on acceptable risk properly belong in the area of risk management. We suggest that, applying quantitative risk assessment methods, recommendations should focus on the number and nature of reactions associated with defined levels of each allergen in food that would permit the definition of risk management measures to provide effective protection for at-risk consumers. The background of the Mandate indicates clearly that the intent behind the FSAI request was ultimately to deploy the growth in knowledge in food allergy. In particular, the mandate recognises, as does an increasing volume of medical and food safety literature that the application of precautionary allergen labelling (PAL) presents major issues for allergic consumers. As currently used, on one hand it jeopardises their safety if the labelling is ignored or on the other hand might limit their choice of available food products. It indicates that a main objective is to reduce, or at least not increase its use. The report would benefit from a more detailed discussion of those terms of reference, leading to an explicit form ulation of the risk management objectives, which could be verified with the mandating authority. We believe that the Opinion would benefit from additional sections describing the risk assessment approach as applied to allergenic foods, including consideration of hazard identification, characterisation and exposure assessment. Adopting this approach would provide a focus that meant that essential elements, such as defining adverse outcomes and reviewing the risk assessment approach to derive conclusions that could serve the risk management objectives, were appropriately discussed. For several allergenic foods, such as peanut, milk, egg and hazelnut several hundred individual Minimum Eliciting Doses exist. These data have been produced in the species of interest (humans), no extrapolation or uncertainty factors are required on that account. It is difficult to understand why no quantitative risk estimates were produced when the data available could be considered of higher quality than much data available for c lassical toxicological risk assessments. Taken in its totality, we are of the view that the draft Opinion is not responding to the entire mandate, which could have been the basis for an effective allergen risk management approach. It will also considerably disadvantage important stakeholders including particularly allergic patients, as well as small and medium-sized companies organisations who will rely on propose quantitative limits, unlike larger organisations which possess the relevant expertise and are able and prepared to develop and apply their own risk assessments.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
1. Introduction	Interassociation des personnes allergiques et intolérantes	EFSA had partially updated its 2004 report. But this draft missed some of the recent publications as Europrevall (European funded project). Some very old studies are still used and might have been updated (line 4836 - Olszewski et al. 1998 for crude peanut oil). It seems that fundamentally, the question is: what kind of food, regarding to its content, a consumer can reasonably wait for when buying its food? Nowadays, in UE, all ingredients that had been voluntary incorporated in the recipe must appear on the ingredients list. Especially, 14 substances or products causing allergies or intolerances, listed in Annex II of 2011/1169 regulation must be labelled even if they are only flavour supports and will be emphasized in ingredient lists as soon as December 13th 2014. But controls show that substances not listed might be present due to process error, label error, cross contamination during process or fraud. IFSA demand for EFSA advice deals not on voluntary included ingredients that regulation deals w ith, but on those unintended ingredients. Two categories might have been looked at but only the first seems to have been considered by the panel: - Standard food: food manufacturers have developed the habit of may contain labels without any regulation. The EFSA scientific opinion is awaited as a basis for definition of "standard food" as we've got a safe food in bacteriological or residue fields; - Food with allegation: what about "free from" food? The market is increasing even if, apart from gluten free, no regulation exists. Consumers note that validation of threshold and analytical method for gluten have driven to an explosion of allegation even on naturally free from gluten food that mustn't wear this mention. The plus value is real for industry as shown by some marketing studies. Today, a consumer buying food labelled "egg free", don't know if it contains less egg than a standard food with no egg in its recipe. May contain (precautionary label): in France, C.N.A. (Conseil National de l'Alimentati on) which aggregate stakeholders of the all food chain, didn't find consensus for may contain label : consumers refuse them, food manufacturers want them. EFSA scientific opinion don't give any answer. - Consumers: for consumers, it is impossible to know if a food with a may contain label really contains or not the ingredient, and even less how much is potentially in it. Several studies showed that consumers don't use those mentions to decide to buy a product. EFSA draft misses to mention studies about accident linked to may contain food consumption, if they exist. - Control bodies: without quantitative threshold, controls drive to food recall as soon as qualitative test is positive (that means at the sensitivity of the methods). But a 20 ppm or 1000 ppm content don't represent the same risk for a sensitive consumer. - Food manufacturers: allergen risk analysis must be part of HACCP. Official thresholds might help, but manufacturers can choose their own threshold. Anyway, this should not drive to labellin g just like in case of bacteriological risk management. For example, nowhere, food is labelled hepatitis E virus free!

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		- Labs: when conceiving a new recipe or a new process, food manufacturer must validate control methods (matrix effect) to be able afterwards to control production. Dosage kits usually dose a characteristic molecule of the ingredient which may not be the or the only allergenic one. As manufacturers use more and more only extracts of ingredients, those kits can't conclude at the absence of the ingredient (ex: cor 8 for hazelnut).The same for yolk or white part of the egg.
1. Introduction	National Food Institute, Technical University of Denmark	The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. The resulting opinion is a 277 page long document. The key issues when having to decide how the unintended presence of allergenic food should be labelled is how to determine a threshold. This very important question is dealt with in chapter 12, a chapter of 3½ pages supplemented by a 4 page table (appendix A).
1. Introduction	National Food Institute, Technical University of Denmark	The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. The resulting opinion is a 277 page long document. The key issues when having to decide how the unintended presence of allergenic food should be labelled is how to determine a threshold. This very important question is dealt with in chapter 12, a chapter of 3½ pages supplemented by a 4 page table (appendix A). Comments to chapter 12 continued: Instead of going critically and detailed into the methods and data used to calculate ED's for allergenic foods the authors dismiss the described results without a comprehensive and in depth argumentation. The situation today is that food allergic patients need to manage their risk on a daily basis. Food producers and public authorities need to do risk assessment of presence of unintended allergenic food. The problem for both groups is the lack of agreed thresholds. It would have been valuable if the EFSA opinion had in depth discussed the pros and cons of the ED approach and contributed creatively to a solution of the present challenges or had contributed with new suggestions on how to develop risk assessment methods in food allergy. It is worth noting that the data available for food allergy risk assessment comes from the relevant species and the persons at risk and not, as many toxicological data, from studies in relatively few rodents. The text in chapter 12 does in no way pay tribute to the uniqueness of the database available. References Madsen CB, Hattersley S, Allen KJ ,Beyer K, Chan C-H, Godefroy SB, Mills ENC, Muñoz-Furlong A, Schnadt S, Ward R, Wickman M, Crevel RWR. Can we define a Tolerable Level of Risk in Food Allergy? Report from a EuroPrevall/UK Food Standards Agency workshop. Clinical and Experimental Allergy, 2012; 42; 30-37

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Madsen CB, Houben, GF, Hattersley, S, Crevel, RWR, Remington, BC, Baumert, JL, From hazard to risk – Assessing the risk: in Madsen CB, Crevel, RWR, Mills, ENC, Taylor SL. Editors. Risk management for food allergy, Elsevier, 2014, ISBN 978-0-12-381988-8
1. Introduction	R-Biopharm AG	595 DNA based are not generally more sensitive than ELISA methods 626 Is Europrevall material on prevalence available?
1. Introduction	R-Biopharm AG	General comments (I have no idea how to put it into this form): The report is only a biased collection of literature. An in-depth evaluation and appraisal is missing especially referring validation by external and independent institutions. The panel members should be chosen more carefully. There is no real decision maker and expert for food allergy and analysis in the group.
1. Introduction	The iFAAM FP7 Project	This section gives a general overview of food allergy and adverse reactions to food, including definitions of terms such as allergen and allergenic ingredient. EFSA comment that the EuroPrevall prevalence data have yet to be published and have not been available to EFSA. The EuroPrevall project partners involved in the EuroPrevall cohort studies have spent considerable time and effort in cleaning and analysing the data sets. Unfortunately this has not been undertaken in a cohesive fashion due to the fragmented and sparse nature of funding for the data cleaning and analysis activity. This will be greatly facilitated by the inclusion of the EuroPrevall data sets into the health informatics platform which is a key activity of the FP7 iFAAM project and we envisage that many papers building on these important data sets will ensue in the next three years. The iFAAM project partnership is developing a regulatory stakeholder group to ensure effective communication of the data and tools arising from the iFAAM project which EFSA will be invited to join and will ensure understanding of these new data. This stakeholder group could help support revision of the EFSA opinion, including understanding of the probabilistic risk assessment models being developed, which builds on nationally funded projects connected to three national organisations with an involvement in risk assessment and regulation, ANSES (FR), DTU (DK) and FSA (UK).
1. Introduction	Università del Piemonte Orientale A. Avogadro, Italy (Institution ex art 36 recognised by EFSA)	PLEASE NOTE THE FOLLOWING TWO COMMENT ARE CORRELATED TO THE PART BEFORE THE "INTRODUCTION": Line 118: the use of modified and quantified plasmid with the insert of a specific food allergen coding region has been also suggested (Ref: D'Andrea M., Coïsson J.D., Travaglia F., GARINO C., Arlorio M. 2009. Development and Validation of a SYBR-Green I Real-Time PCR Protocol to Detect Hazelnut (Corylus avellana L.) in Foods through Calibration via Plasmid Reference Standard. Journal of Agricultural and Food Chemistry 57, 23, 11201-11208) Line 131 "…Gluten" insert: (gliadin fraction) after Gluten
1. Introduction	VITAL Scientific Expert Panel (VSEP)	TERMS OF REFERENCE AS PROVIDED BY THE FOOD SAFETY AUTHORITY OF IRELAND line 603 The Food Safety Authority of Ireland sets out very clearly three broad areas that they wish EFSA to consider (lines 604-607) The prevalence of each allergy in the European Union. Recommendations for threshold concentrations of each allergen in food that would provide an acceptable level of protection

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		for at-risk consumers; The suitability, or otherwise, of qualitative and quantitative DNA-based tests (PCR) for the detection and quantification of food allergens in comparison with immunological (e.g. ELISA) or other methods." (lines 608-613) The mandate clearly has three areas of focus. Prevalence and suitability of analytical methodology are self-explanatory, but the wording around thresholds contains a degree of subjectivity as it involves consideration of "acceptable risk". Decisions on acceptable risk properly belong in the area of risk management, as discussed by Madsen et al (2011). We submit that in responding to the request from FSAI, EFSA should have identified those components relating to risk assessment and, in particular, a request for advice on levels or concentrations of each allergen in food that would support the development of risk management measures by appropriate agencies, to provide effective protection for at-risk consumers. Comment on interpretation of mandateNotwithstanding the ambiguity in the original formulation of the mandate, the background indicates clearly that the intent behind the FSAI request was ultimately to deploy the growth in knowledge in food allergy to improve consumer safety. Specifically it asked the EFSA Panel to review the considerable body of scientific knowledge built in the last 10 years to integrate them into recommendations that can be used to that effect. In particular, the mandate recognises, as does an increasing volume of medical and food safety literature that the application of precautionary allergen labelling (PAL) presents major issues for allergic consumers and, as currently used, jeopardises their safety. It indicates that a main objective is to reduce, or at least not increase its use. We submit that the Panel misdirected itself by interpreting very narrowly the second element of the terms of reference, i.e. derivation of management thresholds, possibly in part because of its phrasing, as discussed above. The report would benefit from a more detailed discussion of those terms of reference, leading to an explicit formulation of the risk management objectives, which could be verified with the mandating authority. In this context, it would be useful to include a discussion/definition on what constitutes an adverse effect in the context of this Opinion. [Note;the Panel has used risk-based terminology in Opinions such as those on exemptions from allergen labelling – e.g. "Panel considers that it is not very likely that N/RBD soybean oils will trigger a severe allergic reaction in susceptible individuals under the conditions of production and use stated by the applica nt. "]. The Panel's report could then have included quantitative estimates of public health impact related to allergen exposure, considering different scenarios, thereby providing a transparent, sound scientific basis for subsequent risk management decisions.
1. Introduction	VITAL Scientific Expert Panel (VSEP)	General comment on overall structure of report line 615 and following The report clearly represents a considerable amount of work, which is wide-ranging in its scope, although possibly more wide-ranging than strictly necessary to address the FSAI request.The overall structure of the report is logical, but would benefit from additional sections describing the risk assessment approach as applied to allergenic foods, including consideration of hazard identification, characterisation and exposure assessment. Adopting this approach would provide a focus that meant that essential elements, such as defining adverse outcomes and reviewing the risk assessment approach to derive conclusions that could serve the risk management objectives, were appropriately discussed, thereby meeting the underlying purpose of the FSAI request .
1. Introduction	VITAL Scientific Expert Panel (VSEP)	Comment on overall approach and conclusions Despite the evident amount of work, the draft report overall remains descriptive and lacks an overall synthesis. A major issue

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		is a lack of transparency over the Panel's selection of data sources and evaluation of data quality. The paucity of quantitative conclusions is disappointing, as well-known approaches in toxicology could have been applied, or at least considered. In particular, it is difficult to understand why no quantitative risk estimates were produced when the data available could be considered of higher quality than much data available for classical toxicological risk assessments. For several allergenic foods, such as peanut, milk, egg and hazelnut several hundred individual Minimum Eliciting Doses exist, produced in the species of interest (humans), and consequently no extrapolation or uncertainty factors are required on that account. The Panel makes the valid point that certain individuals (those with a prior history of severe reaction, irrespective of dose, which is not necessarily synonymous with most sensitive) are often excluded from challenges, which could influence the shape of dose-distribution curves and therefore any benchmarks (e.g. reference doses) derived from these curves. The Panel then uncritically uses this argument to dismiss any attempt at deriving quantitative benchmarks. Similarly, the Panel notes that challenges are conducted under standardised conditions, rather than the diverse conditions under which reactions may occur in community settings but fails to acknowledge that an equivalent situation occurs in standard toxicological bioassays in animals, in which the test substance is administered to healthy young animals in controlled conditions, not to animals in undocumented or compromised health. The Panel rightly recognises that avoidance of the implicated allergenic food is the basis for management, but does not take this observation to its logical conclusion, namely that labelling is a critical component. As a result the Panel does not recognise the role of voluntary precautionary allergen labelling (PAL), the credibility of which depends on its appropriate and circumspect use, which requires common, agreed standards for industry and authorities to work to. There is general recognition within the food industry, allergy support groups and clinicians that standards for PAL are critical to allergen and allergy risk management and must be based on risk assessment. It is rather surprising that the Panel have not pursued this aspect more thoroughly, with the consequence that they may have missed the opportunity to review critically their approach to and conclusions on thresholds.Taken in its totality, we submit that the draft Opinion is incomplete and in its current form may considerably disadvantage key stakeholders including particularly allergic consumers, as well as food businesses through the lack of a uniform Commission endorsed risk based approach to voluntary precautionary allergen labelling.This submission will provide information on the risk assessment approach by the VITAL® Scientific Expert Panel in making recommendations to the Australian Allergen Bureau's VITAL® system for voluntary precautionary incidental allergen labelling. VITAL® has been in use by the food industry in Australia and New Zealand since 2007
2. Classification of adverse reactions to foods and definition of terms	AFDIAG	Comment n°2 – lines 22 to 140 (summary) EFSA had partially updated its 2004 report. But this draft missed some of the recent publication as Europrevall (European funded project). Some very old studies are used and might have been updated (line 4836 - Olszewski et al. 1998 for crude peanut oil). Normalization is also on process in dosage field and might had take profit of EFSA scientific expertise. For allergic consumers and their relative as well as people in contact with them, uncertainty is the key point. Food label aims to reduce uncertainty but may contain warning increase it. If official thresholds were established for quality management systems, food manufacturers might avoid sale "contaminated" products the way they do with bacteriological hazards. Commission will not be able easily to derive any decision from this draft.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Can the panel propose clear definitions (and clear connection between them) about different kinds of threshold aimed at (individual, population, control, quality manageme nt, free from…) safe (as in "safe allergen threshold level") risk/Benefice of unintended ingredient label severity of reactions. Effectively we've got allergy to die from (oedema, anaphylaxis, asthma) with impressive reaction and fatalities but food regulators must also take in account allergies to live with (atopic dermatitis, urticarial, belly ache…) because of quality of life and long term associated risks. Those represent an heavy burden either at an individual or at a collective level (health costs). EFSA panel estimates that threshold for gluten (20 ppm for gluten free in specific food like bread, flour, biscuits, 100 ppm for low level of gluten) relieve burden on coeliac consumers. Panel also mention the 10 ppm threshold already mandatory for sulphate. Could it, for example, give an advice protecting 99,9% of European population for some ingredients of the annexe list to go on even if it is not yet possible for all of them ? The report could include some data about the RASFF 2013 repor t. The RASFF report of 2013 lists 53 cases of food poisoning. One is linked to undeclared ingredient on standard food (1-50 ppm casein, 0,61-2,5 ppm lactalbumine) and another to milk in "free from" chocolate (510 ppm). But 10 had been caused by histamine (1000 to 4375 ppm…!) also known to emphasize allergic reactions (asthma fatalities for example). On the 3137 notification, Allergens are pointed in 71 cases (0,02%) nearly the same that 76 GMO/novel food for example. Another interesting point give us data about the sensitivity of the subject. ON those 3137 notifications, 410 had came from industry (13%) but for allergen, this industry notifications reach 25 (35%). ON the total, 118 notifications came from consumers complain (3,76%) but for allergen 14 came from consumers (19,7%). In general, 29 % of notifications came from official controls in the market but for the allergens, this share is 42%. Border control and control in non member states are much more low for allergens than in other hazards.
2. Classification of adverse reactions to foods and definition of terms	EAACI	This section importantly lays out the definitions of terms used in the Opinion. We suggest that these be harmonised with those provided in Muraro et al (Allergy 2014 69(8):1008-25). The latter have a clear scientific basis and have been agreed by a large group of scientific and clinical experts. For example the definition of an allergen (p15, line 631) used by EFSA is at variance with that developed by EAACI. The EAACI definition has the benefit of explicitly defining the biological activity of an allergen and it nature whilst the EFSA definition is limited only to proteins and peptides and does not explicitly relate to either IgE or cellular immune responses. This definition could miss important allergenic moieties, including carbohydrates such as alpha-galactose involved in causing allergies to meat. Such discrepancies should be minimised and if there is a

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		variance an explanation given as to justify and clarify why different definitions have been applied. If not explained will cause confusion in the communi ty.
2. Classification of adverse reactions to foods and definition of terms	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	The panel of experts should have proposed clear definitions of: − different kinds of threshold (individual, population, control, quality management, "free from"); − safe (as in "safe allergen threshold level"); − risk/benefit of unintended ingredients label; − severity of reactions: people might die from allergy (anaphylaxis, asthma), but food regulators must also take into account quality of life of and long term associated risks for patients with less severe allergies (atopic dermatitis, urticarial) as they represent a heavy burden both at an individual and a collective level (due to the high health costs).
2. Classification of adverse reactions to foods and definition of terms	Familles Rurales	Can the panel propose clear definitions (and clear connection between them) about: - Different kinds of threshold aimed at (individual, population, control, quality management, free from…) - Safe (as in "safe allergen threshold level") - Risk/Benefice of unintended ingredient label - Severity of reactions. Effectively we've got allergy to die from (oedema, anaphylaxis and asthma) with impressive reaction and fatalities but food regulators must also take into account allergies to live with (atopic dermatitis, urticarial, belly ache…) because of quality of life and long term associated risks. Those represent a heavy burden either at an individual or at a collective level (health costs).
2. Classification of adverse reactions to foods and definition of terms	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
2. Classification of adverse reactions to foods and definition of terms	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals?

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
2. Classification of adverse reactions to foods and definition of terms	Interassociation des personnes allergiques et intolérantes	Can the panel propose clear definitions (and clear connection between them) about: - Different kinds of threshold aimed at (individual, population, control, quality management, free from…) - Safe (as in “safe allergen threshold level”) - Risk/Benefice of unintended ingredient label - Severity of reactions. Effectively we’ve got allergy to die from (oedema, anaphylaxis and asthma) with impressive reaction and fatalities but food regulators must also take into account allergies to live with (atopic dermatitis, urticarial, belly ache…) because of quality of life and long term associated risks. Those represent a heavy burden either at an individual or at a collective level (health costs).
2. Classification of adverse reactions to foods and definition of terms	National Food Institute, Technical University of Denmark	Glossary Sensitisation Positive SPTs or high levels of specific IgE to the offending food Suggestion: delete “high levels of” or define it
2. Classification of adverse reactions to foods and definition of terms	The iFAAM FP7 Project	An important aspect of this section is to request harmonisation of definitions. The European Academy of Allergy and Clinical Immunology (EAACI) has developed such definitions as part of the development of the Food Allergy Guidelines (Muraro et al, Allergy 2014 69(8):1008-25) but the definitions differ from those applied by EFSA. An example of this is the definition of an allergen (p15, line 631) used by EFSA which is limited to proteins and peptides and does not explicitly relate to either IgE or cellular immune responses, whilst the definition used by EAACI explicitly refers to the nature of the biological response which turns a protein into an allergen. The definition applied by EFSA misses important allergenic moieties, including carbohydrates such as alpha-galactose involved in causing allergies to meat. Such discrepancies should be minimised and if there is a variance, an explanation given as to justify and clarify why different definitions have been applied. If not explained this will cause needless con fusion in the community.
3. Clinical symptoms of food allergy	DANONE	Lines 682-894 : An estimate of the relative proportions of reactions associated with each symptom would help to assess the public health impact.
3. Clinical symptoms of food allergy	EAACI	The comment relating to classification of adverse reactions to foods is followed in the section on clinical symptoms and disease definitions. For example, Heiner syndrome has been included by EFSA as a form of asthma (line 832) and whilst described appropriately should not be classified under a heading of asthma. In some instances there is a lack of clarity as to which symptoms can be attributed to IgE-mediated food allergy.
3. Clinical symptoms of food allergy	Faculty of Medicine, NANCY France - Consultant in the	All of these comments are related to the clinical presentation of food allergies that is clearly unsufficient 1. it is necessary to include a short chapter (after "urticaria and angioedema"): exercise induced food allergies: either

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
	Allergy dDpartment Hospital Center EPINAL Fra	urticaria or angioedema , or anaphylactic shock, are more and more frequent, enhanced by the intake of certain drugs or by alcohol, to various allergens, most of them being related to gluten or wheat ns LTP or gluten isolates. 2. It is mandatory to include a chapter for eosinophilic esophagitis, an emergent allergic disease in children as well as in adults however to a lesser frequence. I guess that there are more than 300 references about this topic ! Personally I have seen more than twenty cases in the previous years! 3. Laryngeal oedema: symptoms have to be underlined: inspiratory dyspnea, hoarse voice then aphonia and most of the time uvular angioedema and salivary dysphagia are associated. it is not always associated to other symptoms if it occurs in food allergic adults that undergo a treatment by conversion enzyme inhibitors. 4. Not a single word about the new entity of semi-delayed anaphylaxis to mammal meats by the way of a sensitization to alphagalactose! There are numerous cases in USA Australia France Belgium and probably other countries (central Europa). page 23: ALL food allergic children deserve the evaluation of a latent bronchial hyperreactivity , since lethal acute asthma may occur even in non asthmatic patients. page 25-26 Epidemiology: a recent reference has to be added: Prescott, 2014 page 28 Prevalence of allergy to various foods: please go to www.allergyvigilance.org: it is a scientific validated site for food allergies. you will find statistics from this netwotk giving the incidence of all foods. (http://www.allergyvigilance.org/activites-du-rav/235-statistique-2013-anaphylaxie-alimentaire-grand-public) ethnicity can you give information about the studies from USA showing the difference between caucasian, hispanic and african peop le, since immigrants take part in the european societies.
3. Clinical symptoms of food allergy	Familles Rurales	For allergic consumers and their relative as well as people in contact with them, uncertainty is the key point and the main trigger to manage their day to day live. Uncertainty is a huge burden for Quality of life as several scientific studies showed. Food label aims to reduce uncertainty but may contain warning increase it. If official thresholds were established for quality management systems, food manufacturers might avoid sale “contaminated” products the way they do with bacteriological hazards. EFSA panel estimates that threshold for gluten (20 ppm for gluten free in specific food like bread, flour, biscuits, 100 ppm for low level of gluten) relieve burden on coeliac consumers. Panel also mention the 10 ppm threshold already mandatory for sulphate. Could it, for example, give an advice protecting 99,9% of European population for some ingredients of the annexe list to go on even if it is not yet possible for all of them ? The report could include some data about the RASFF 2013 report. The RASFF report of 2013 lists 53 cases of food poisoning. One is linked to undeclared ingredient on standard food (1-50 ppm casein, 0.61-2.5 ppm lactalbumine) and another to milk in “free from” chocolate (510 ppm). But 10 had been caused by histamine (1000 to 4375 ppm…!) also

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		known to emphasize allergic reactions (asthma fatalities for example). On the 3137 notifications, allergens are pointed in 71 cases (0.02%) nearly the same that 76 GMO/novel food for example. Another interesting point give us data about the sensitivity of the subject. On those 3137 notifications, 410 had come from industry (13%) but for allergen, this industry notifications reach 25 (35%). On the total, 118 notifications came from consumers complains (3.76%) but for allergen 14 came from consumers (19.7%). In general, 29 % of notifications came from official controls in the market but for the allergens, this share is 42%. Border control and control in non-member states are much lower for allergens than in other hazards.
3. Clinical symptoms of food allergy	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
3. Clinical symptoms of food allergy	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
3. Clinical symptoms of food allergy	FoodDrinkEurope	3 – Clinical symptoms of food allergy (lines 682-894) The description of symptoms is comprehensive, although it is sometimes not clear which are attributable to IgE-mediated reactions, which are the public health outcome of concern, and which are due to other mechanisms, The section would also be enhanced by an estimate of the relative proportion of reactions associated with each group of symptoms. This would help the evaluation of public health impact.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Is the last paragraph of the introductory subsection consistent with the EFSA AFC Panel's previous conclusions on the Southampton study on additives (EFSA J 2008)?
3. Clinical symptoms of food allergy	Food & Drink Federation	(lines 682-894) The description of symptoms is comprehensive, although it is sometimes not clear which are attributable to IgE-mediated reactions, which are the public health outcome of concern and which are due to other mechanisms. This section would benefit from an estimate of the relative proportion of reactions associated with each group of symptoms, which would aid the evaluation of public health impact.
3. Clinical symptoms of food allergy	SPAIC: Portuguese Society of Allergology and Clinical Immunology	Line 685: In Table 1, I think must be included contact dermatitis within the skin manifestations. (Burks AW, Tang M, Sicherer S, Muraro A, Eigenmann PA, Ebisawa M, Fiocchi A, Chiang W, Beyer K, Wood R, Hourihane J, Jones SM, Lack G and Sampson HA, 2012b. ICON: food allergy. J Allergy Clin Immunol, 129, 906-920). Similarly, should online added on line 755 that contact dermatitis usually appears regarding food handling involved, either occupationally in the case of food industry workers (Múgica, Añíbarro, Seoane and Lombardero, 2003. Contact urticaria by angler fish. Allergy;58:682-683 and Lopata AL, Jeebhay MF, 2013. Airborne seafood allergens as a cause of occupational allergy and asthma. Curr Allergy Asthma Rep. 2013 Jun;13(3):288-97) as accidentally in other cases. (Monti, Bonfante, Muratore, Peltran, Oggero, Silvestro and Mussa, 2003. Kiss-induced facial urticaria in a child allergic to fish. Allergy;58:684-685). Line 836: In my opinion, should be added that in some particularly sensitive individuals, c an trigger an asthma attack after inhalation of steam cooking of some foods, especially fish and seafood. (Crespo, Pascual, Domínguez, Ojeda, Muñoz and Martín- Esteban. Allergic reactions associated with airbone fish particles in IgE-mediated fish hypersensitive patients, 1995. Allergy;5:257-261; Rodríguez J, Reaño M, Vives R, Canto G, Daroca P, Crespo JF, Vila C, Villarreal O and Bensabat Z, 1997. Occupational asthma caused by fish inhalation. Allergy,52, 866-869; Leonardi S, Pecoraro R, Filippelli M, Miraglia Del Giudice M, Marseglia G, Salpietro C, Arrigo T, Stringari G, Ricò S, La Rosa M and Caffarelli C. 2014. Allergic reactions to foods by inhalation in children. Allergy Asthma Proc. Jul;35(4):288-94 and Lopata AL, Jeebhay MF, 2013. Airborne seafood allergens as a cause of occupational allergy and asthma. Curr Allergy Asthma Rep. 2013 Jun;13(3):288-97)
3. Clinical symptoms of food allergy	The iFAAM FP7 Project	The comment relating to classification of adverse reactions to foods is followed in the section on clinical symptoms and disease definitions. For example, Heiner syndrome whilst correctly described, should not be classified as a type of asthma.
4. Diagnosis of food allergy	Familles Rurales	line 2346 and after Report readers might benefit of EFSA panel scientific expertise about validation of dosage methods prior to new recipe production (matrix effect) and routine check. An analytical result only based on kit application without real validation is of no use. Normalization is on the way but seems out of the general threshold discussion for the moment. Could Efsa expert provide their opinion on this Normalization ?
4. Diagnosis of food allergy	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
4. Diagnosis of food allergy	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
4. Diagnosis of food allergy	FoodDrinkEurope	4 - Diagnosis of food allergy (lines 895-1019) This section is a good overview of the subject. However, Grimshaw et al (2003) cited in the subsection on SPT, observations refer to the effect of food matrices containing different concentrations of fat on the thresholds of reactivity in food challenges.
4. Diagnosis of food allergy	Food & Drink Federation	(lines 895-1019) This section provides a good overview. However, the observations of Grimshaw et al (2003), cited in the subsection on skin prick tests, refer to the effect of food matrices containing different concentrations of fat on the thresholds of reactivity in food challenges.
4. Diagnosis of food allergy	The iFAAM FP7 Project	This section notes that there is a need to increase standardisation of food challenges and materials used for skin testing and associated protocols. However, notable related current activities by EAACI and AAAAI in this arena, e.g the Practall consensus paper on double blind placebo controlled food challenges (Sampson et al JACI 2012, 130:1260-74) and the contents of the food allergy guidelines (Muraro et al Allergy 2014 69(8):1008-25; Soares-Weiser et al Allergy 69(1):76-86.) are omitted. The section on measurement of food specific IgE is incomplete. Available tests other than RAST are ignored. There is no discussion of other methods anda major leading commercially available test (ImmunoCAP) is not mentioned (section 4.1.1. line 932) and alluded to only peripherally (line 1000) despite having been widely used since the 1990's. The Grimshaw et al (2003) reference is incorrectly cited in the subsection on SPT, as the main thrust of this paper is the effect of food matrices containing different concentrations of fat on the thresholds of reactivity in food challenges.
4. Diagnosis of food	Università del	Lines 997-999: "The measurement of IgE against specific components of allergens, named components-resolved allergy

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
allergy	Piemonte Orientale A. Avogadro, Italy (Institution ex art 36 recognised by EFSA)	diagnosis (Vieira et al., 2012) is not yet able to discriminate between sensitisation and clinically relevant food allergy (Ebo et al., 2010b)". PLEASE NOTE: In several cases sensitization is associated with objective symptoms, therefore CRD does provide such information (Ref: Masthoff L.J.N., Mattsson L., Zuidmeer-Jongejan L., Lidholm J., Andersson K., Akkerdaas J.H., Versteeg S.A., GARINO C., Meijer Y., Kentie P., Versluis A., den Hartog Jager C.F., Bruijnzeel-Koomen C.A.F.M., Knulst A.C., van Ree R., van Hoffen E., Pasmans S.G.M.A. 2013. Sensitization to Cor a 9 and Cor a 14 is highly specific for a severe hazelnut allergy in Dutch children and adults. Journal of Allergy and Clinical Immunology 132, 393-399).
5. Management of food allergy	DANONE	Lines 1021-1028 : Avoidance is based on a fair and relevant information of consumer mainly through labelling. In this context precautionary allergen labelling is critical for consumer protection and requires quantitative standards based on risk assessment to define when and how precautionary labelling should be used. Deeper assessment of this issue would have been helpful.
5. Management of food allergy	Deutscher Allergie- und Asthmabund	Lines 1020 - 1072 1. The recently published EAACI Guidelines on Food Allergy Management were not considered. Since they provide a comprehensive picture, it would be worth to include them in the EFSA Opinion Muraro A et al Allergy 2014 69(8): 1008-25 and 1046-57 and 10.1111/all.12453 2. Quality of life Food allergy is a chronic disease, which has impact on Quality of life for affected people. Since establishment of tools that are disease specific this impact can be measured and a considerable number of publications are available. None of them has been considered by the Panel, so that Quality of life, which is a major aspect in research studies today, has not been included in the EFSA Opinion. Lines 1021 – 1025 The EFSA Opinion correctly states that "dietary avoidance of specific allergenic foods … is the mainstay of management in IgE-mediated and non-IgE-mediated food allergy", but does not take food labelling and allergen information into consideration. Allergic consumers are only able to avoid thei r specific food allergen, if the allergen information they receive from the food manufacturer on the label is accurate, clear, reliable and consistent. Whilst the use of allergenic food as ingredients is mandatory and regulated, there are currently no universally agreed standards by which unintended presence of allergens is evaluated. As a result Precautionary Allergen Labelling (PAL) is not applied according to standards that would demonstrate transparency and confidence in its presence or absence. The allergic consumer is therefore currently unable, effectively and reliably, to avoid specific allergenic foods due to the shortcomings of PAL. The current use of PAL results in uncertainty and dissatisfaction, since allergic consumers are unable to judge from looking at the labelling of a food product whether: a) A PAL does or does not carry a genuine risk of cross contamination b) The absence of PAL does or does not indicate a "safe" product. Consequently, an informed assessment and choice to maxim ise the protection of each allergic consumer's health and safety is not possible.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Allergic consumer/ patient groups, clinicians as well as National and International Allergy Organisations, such as EAACI (in the EU) and WAO (globally), see the need for mandatory standards on allergen and allergy-risk management based on an agreed and consistent method of allergy risk assessment. Allen KJ et al, 2014 Precautionary labelling of foods for allergen content: are we ready for a global framework? World Allergy Organization Journal 2014, 7:10 Muraro A et al, 2014 Protecting Consumers with food allergies – EAACI Guidelines Allergy. 2014 May 30. doi: 10.1111/all.12453 The current labelling practices in regard to PAL also have impact on quality of life, which should also be included in the evaluation. DunnGalvin et al. 2014 Living with Food Allergy: Cause for Concern in : Risk , Management for Food Allergy, Charlotte B. Madsen (Ed). US; Elsevier. DunnGalvin A, & Hourihane JO'B. Developmental trajectories in aller gic diseases: A review. Advances in Food and Nutrition Research, 2009 c. Volume 56 Elsevier Inc. DunnGalvin, A & Hourihane, J O'B. Developmental aspects of HRQL in food related chronic disease (2011) The International Handbook of Behaviour, Diet and Nutrition; Springer, US As the Panel states in Opinion in Lines 2765–2767 in its considerations for coeliac disease "limit values … help managing the diet of most coeliac patients effectively" This also applies for the management of allergic consumers. A considered assessment by EFSA of new scientific information could assist in developing a harmonised approach to protecting vulnerable consumers in the EU particularly with regard to PAL as addressed by the IFSA in its mandate.(s.chapt.12)
5. Management of food allergy	EAACI	The sections on diagnosis notes there is a need to increasing standardisation of food challenges and materials used for skin testing and associated protocols. The opinion does not include up-to-date information on efforts being made by EAACI and AAAAI in this arena, notably the Practall consensus paper on double blind placebo controlled food challenges (Sampson et al JACI 2012, 130:1260-74) and the Food Allergy Guidelines on diagnosis (Muraro et al Allergy 2014 69(8):1008-25; Soares-Weiser et al Allergy 69(1):76-86.). The section on measurement of food specific IgE is restricted to RAST and no discussion is made of other methods or a major leading commercially available test – ImmunoCAP – is not mentioned (section 4.1.1. line 932). The EAACI guidelines acknowledge that whilst not standardised, specific IgE and SPT are scientifically valid tests. This point should be considered in the opinion (lines 1006-1019) and that the community is moving towards standardisation.
5. Management of food allergy	EAACI	Crucially no aspect relating to the impact of food allergy on quality of life is described and appears absent from the opinion. Currently the ESA opinion devotes five lines (1022-1028) to food allergen avoidance and yet it is the most complex and difficult thing for patients to manage, especially when eating out of the home. The impact of food allergy on quality of life should be included in the Opinion for which there are now many papers, including two from the EAACI guidelines (Muraro et al Allergy 2014 69(8): 1008-25 and 1046-57 and 10.1111/all.12453). No consideration is given to the management of anaphylaxis. This is a considerable omission in the section and a revision and should build on the consensus from EAACI as described in Dhami et al Allergy 2014 Feb;69(2):168-75. Food allergy is a relatively new condition and as a consequence

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		little is knowledge of the long term effects of the condition. This was identified by the EAACI Food Allergy Guidelines group as a significant gap in knowledge (de Silva et al Allergy. 2014 69(2):159-67.). The EFSA opinion discusses therapeutic options. We would like to bring to the attention of EFSA the systematic review of data undertaken by the EAACI Guidelines group on this topic. The guidelines group concluded that, whilst early studies using oral immunotherapy are encouraging, quality of the evidence base is questionable and the treatment is often associated with adverse effects. de Silva et al (Allergy. 2014 69(2):159-67) identified that further research was required to explore whether the benefits of treatment continue after the intervention is stopped, as data in this regard are especially sparse.
5. Management of food allergy	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	Labelling is a crucial aspect for a good management of food allergy, as it allows allergy patients to be fully awared of the choices they make and, thus, it contributes to a better control of the disease.
5. Management of food allergy	FAMILLES RURALES	line 2515 and after EFSA panel concludes: "current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer". For reasons pointed in our previous comment, thresholds are needed for quality management purposes (not necessary linked with may contain label) either as a voluntary decision of food manufacturer or as an official decision. As EFSA points that it can't establish thresholds based on epidemiology, can it suggest other means? For example, consumers and control bodies might take advantage of better knowledge on reality of cross contamination in food manufacturers facilities (like UE knows in animal feed production). They also might take advantage of enquiry on other countries (Switzerland, Japan, New Zealand and Australia).
5. Management of food allergy	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
5. Management of food allergy	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this?

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
5. Management of food allergy	FoodDrinkEurope	5 - Management of food allergy (lines 1020- 1072) 5.1 - Allergen avoidance (lines 1021-1028) It is correctly recognised that avoiding exposure to the offending allergen(s), whether intentionally or unintentionally present in the food, is a mainstay of allergy management. This implies that the integrity of labelling, including precautionary allergen labelling (PAL) is critical to protection of the allergic consumer. This integrity can only be assured if consumers trust those labels and act on them, which requires that standards exist to define the basis on which they should be used. It is now widely recognised that for PAL those standards must be quantitative and based on risk assessment. Deeper scrutiny of this issue would have been helpful and enhance transparency. The Panel suggests that breast-feeding mothers should avoid eating any allergenic food to which their babies have reacted, citing a 1986 paper in support. This advice appears to contradict international consensus in this area (Burks et a l 2012) which cites among other statements: The NIAID guidelines further recommend that all infants be exclusively breast-fed, without maternal diet restriction of allergens, until 4 to 6 months of age, unless breast-feeding is contraindicated for medical reasons.[also cited by in Opinion elsewhere].
5. Management of food allergy	Food & Drink Federation	5.1 - Allergen avoidance (lines 1021-1028) The Opinion recognises that avoiding exposure to the offending allergen(s), whether intentionally or unintentionally present in the food, is key to allergy management. By implication, the integrity of labelling, including precautionary allergen labelling (PAL) is critical to protect the allergic consumer. Therefore, consumers need to trust and act on such labelling, which requires that standards exist to define the basis on which they should be used. It is now widely recognised that for PAL, those standards must be quantitative and based on risk assessment. Further consideration of this issue within the opinion would have been extremely helpful. The Panel suggests that breast-feeding mothers should avoid eating any allergenic food to which their babies have reacted, citing a 1986 paper in support. This advice appears to contradict international consensus in this area (Burks et al 2012) which cites among other statements: The NIAID guidelines further recomme nd that all infants be exclusively breast-fed, without maternal diet restriction of allergens, until 4 to 6 months of age, unless breast-feeding is contraindicated for medical reasons.
5. Management of	Interassociation des	For allergic consumers and their relative as well as people in contact with them, uncertainty is the key point and the main

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
food allergy	personnes allergiques et intolérantes	trigger to manage their day to day live. Uncertainty is a huge burden for Quality of life as several scientific studies showed. Food label aims to reduce uncertainty but may contain warning increase it. If official thresholds were established for quality management systems, food manufacturers might avoid sale “contaminated” products the way they do with bacteriological hazards. EFSA panel estimates that threshold for gluten (20 ppm for gluten free in specific food like bread, flour, biscuits, 100 ppm for low level of gluten) relieve burden on coeliac consumers. Panel also mention the 10 ppm threshold already mandatory for sulphate. Could it, for example, give an advice protecting 99,9% of European population for some ingredients of the annexe list to go on even if it is not yet possible for all of them ? The report could include some data about the RASFF 2013 report. The RASFF r eport of 2013 lists 53 cases of food poisoning. One is linked to undeclared ingredient on standard food (1-50 ppm casein, 0.61-2.5 ppm lactalbumine) and another to milk in “free from” chocolate (510 ppm). But 10 had been caused by histamine (1000 to 4375 ppm…!) also known to emphasize allergic reactions (asthma fatalities for example). On the 3137 notifications, allergens are pointed in 71 cases (0.02%) nearly the same that 76 GMO/novel food for example. Another interesting point give us data about the sensitivity of the subject. On those 3137 notifications, 410 had come from industry (13%) but for allergen, this industry notifications reach 25 (35%). On the total, 118 notifications came from consumers complains (3.76%) but for allergen 14 came from consumers (19.7%). In general, 29 % of notifications came from official controls in the market but for the allergens, this share is 42%. Border control and control in non-member states are much lower for allergens than in other hazards.
5. Management of food allergy	The Allergen Bureau Ltd	5.1 - Allergen avoidance (lines 1021-1028) The Panel correctly recognises that avoiding exposure to the offending allergen(s), whether intentionally or unintentionally present in the food, is a mainstay of allergy management. This implies that the integrity of labelling, including precautionary labelling for allergens unavoidably present due to cross-contact is critical to protection of the allergic consumer. This integrity can only be assured if consumers trust those labels and act on them, which requires that protocols, either voluntary or mandatory exist, to define the basis on which they should be used. It is now widely recognised that standards for precautionary labelling must be quantitative and based on risk assessment. Deeper scrutiny of this issue by the Panel would have been helpful and enhanced transparency. The Australian Allergen Bureau’s VITAL® system provides an example of an effective risk based system for precautionary labelling of cross-contact allergens that has been developed and imp lemented by the food industry in Australia and New Zealand to address these issues since 2007[www.allergenbureau.net/vital/] . VITAL® was developed within the Australian/New Zealand food regulatory environment. The Australia New Zealand Food Standards Code Standard 1.2.3 requires the mandatory labelling of the following allergen foods or products derived from them when present as a result of having been added as an ingredient; a food additive; a processing aid; or or component of one of these. However, there is no regulatory requirement for labelling of allergens present due to incidental factors, such as cross-contact during manufacturing or handling.
5. Management of food allergy	The iFAAM FP7 Project	Consideration of the impact of food allergy on quality of life appears to be absent from the opinion. The EuroPrevall project developed the first ever suite of instruments for assessing the impact of food allergy on quality of life for individuals

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		including adults, teenagers, and families of young children (de Blok BM et al Allergy. 2007 Jul;62(7):733-7; Flokstra-de Blok et al J Allergy Clin Immunol. 2008 Jul;122(1):139-44; Flokstra-de Blok et al Clin Exp Allergy. 2009 Jan;39(1):127-37; Flokstra-de Blok et al Allergy. 2010 Aug;65(8):1031-8; van der Velde et al J Allergy Clin Immunol. 2012 Nov;130(5):1136-1143; DunnGalvin et al Clin Exp Allergy. 2008 Jun;38(6):977-86; DunnGalvin Clin Exp Allergy. 2010 Mar;40(3):476-85; van der Velde et al Qual Life Res. 2009 Mar;18(2):245-51). There is also data on the economic impact of food allergies which should be included (Fox et al Eur J Public Health. 2013 Oct;23(5):757-62). This activity was a major achievement of the EuroPrevall project. Currently the ESA opinion devo tes five lines (1022-1028) to food allergen avoidance and yet it is the most complex and difficult thing for patients to manage, especially when eating out of the home. A section devoted to this topic should be included. Management of anaphylaxis is not considered, a significant omission which should be addressed in any revision of the Opinion. Avoiding exposure to the offending allergen(s), whether intentionally or unintentionally present in the food, is a mainstay of allergy management and hence the integrity of labelling, including precautionary allergen labelling (PAL) which is critical to the protection of the allergic consumer. This integrity can only be assured if consumers trust those labels and act on them, which requires that standards exist to define the basis on which they should be used. It is now widely recognised that for PAL those standards must be quantitative and based on risk assessment. Deeper scrutiny of this issue by the Panel should be considered to make the Opinion a more complete document and support the EU Commission to achieve the goal set out in Food Information Regulation 1169/2011 that consumers must be able to make informed food choices. Food allergy is a relatively new condition and as a consequence little is knowledge of the long term effects of the condition. This was identified by the EAACI Food Allergy Guidelines group as a significant gap in knowledge (de Silva et al Allergy. 2014 69(2):159-67.). The EFSA opinion discusses therapeutic options. However, the systematic review of data undertaken by the EAACI Guidelines group indicate that whilst early studies using oral immunotherapy are encouraging, quality of the evidence base is questionable and the treatment is often associated with adverse effects. de Silva et al (Allergy. 2014 69(2):159-67) identified that further research was required to explore whether the benefits of treatment continue after the intervention is stopped, as data in this regard are especially sparse.
5. Management of food allergy	VITAL Scientific Expert Panel (VSEP)	5.1 - Allergen avoidance lines 1021-1028 The Panel correctly recognises that avoiding exposure to the offending allergen(s), whether intentionally or unintentionally present in the food, is a mainstay of allergy management. This implies that the integrity of labelling, including precautionary allergen labelling (PAL) is critical to protection of the allergic consumer. This integrity can only be assured if consumers trust those labels and act on them, which requires that standards exist to define the basis on which they should be used. It is now widely recognised that for PAL those standards must be quantitative and based on risk assessment. Deeper scrutiny of this issue by the Panel would have been helpful and enhanced transparency. The Australian Allergen Bureau's VITAL system provides an example of an established effective risk based system for PAL [www.allergenbureau.net/vital/]
6. Epidemiology of food allergy	DANONE	Lines 1166-1262 : The terms of reference were on allergen included in Directive 2007/68/EC. It is unclear why other allergens not included in this list have been included in this prevalence approach. It would have been useful to introduce the rationale used to include (or exclude) particular foods within the scope of this

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		section together with the assessment of public health impact.
6. Epidemiology of food allergy	Deutscher Allergie- und Asthmabund	Lines 1113 - 1133 Two European meta-analyses provide data for epidemiology and prevalence of food allergy in Europe and should be included 1. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62-75. 2. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992-1007. Lines 1166 – 1262 It is not obvious why the Panel chose the currently evaluated selection of food not listed in Annex III a Why were strawberries and citrus fruits chosen, but not peach or apple? Meat as allergenic food and fairly new entity in food allergies due to a-Gal is not mentioned in this chapter Lines 1268 – 1270 It is concluded that 50% of allergic reactions among adults are due to fruits of the latex group and of to the Rosaceae family, vegetables of the Apaceae family, and various nu ts and peanuts. Anaphylactic reactions have been reported to foods not included in Annex IIIa. It is not mentioned if the Panel considers it necessary that specific foods should be added to Annex IIIa
6. Epidemiology of food allergy	EAACI	Nwaru et al (Allergy 2014 69 62-75) is a meta-analysis of food allergy prevalence that specifically consider the European perspective and concluded that the frequency of IgE-mediated food allergy is higher among children than among adults and highest in North Western Europe than in other regions, while Southern Europe seems to have the lowest prevalence. A lack of studies in the south of Europe was noted in this publication. Nwaru et al concluded that the prevalence of self-reported food allergy is 6.9% in children and 5.1% in adults, with the prevalence of challenge-proven food allergy estimated as 0.9%. Such data should be included in any revision of the EFSA opinion. The Opinion would benefit from clearly defining where data are included which are drawn from unselected populations using rigorous diagnostic procedures and those which are drawn from outpatient clinic subjects and may only undertake diagnosis using a clinical history without a food challenge. This is not clear throughout the document and dat a presented in the opinion are often confused. Only one of the previous studies examined the time trends in the frequency of food allergy and concluded that it is unclear whether the prevalence is increasing. The observed increase over time could be attributed to increased awareness and improved pattern of reporting and diagnosis rather than a true increase respectively. A review of data available on the prevalence of serious IgE-mediated adverse reactions would be useful to include capitalising on the data that is available in certain member states e.g. the German Anaphylaxis Registry.
6. Epidemiology of food allergy	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	It would have been useful if the experts included estimates of incidence, including data from serious adverse reaction registries to further assess the public health impact of food allergy. In addition, some new data on the prevalence of asthma with rates now around 30% should be mentioned. The RASFF – the Rapid Alert System for Food and Feed report of 2013 shows 53 cases of food poisoning. One is linked to undeclared ingredient on standard food (1-50 ppm casein, 0,61-2,5 ppm lactalbumine) and another to milk in "free from" chocolate (510 ppm), but more that 10 have been caused by histamine (1000 to 4375 ppm). Out of the 3137 notification,

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		allergens are pointed in 71 cases (0,02%), nearly the same as 76 GMO/novel food. 410 notification come from industry (13%), but for allergen these industry notifications reach 25 (35%). 118 notifications come from consumers complain (3,76%), while for allergen 14 come from consumers (19,7%). More in general, 29% of notifications come from official controls in the market, b ut for allergens this share is 42%. Border control and control in non-Member States are much lower for allergens than for other hazards.
6. Epidemiology of food allergy	FEDIOL	Section 6.5 refers to the prevalence of allergy to foods not listed in Annex IIIa, assessing certain food categories. FEDIOL believes that this section should be clarified. Specifically, criteria for consideration of a food/food group need to be explicit, as does the basis for any conclusions that are drawn. It would be highly desirable to have concluding remarks regarding the public health importance of each food/food group, related to the quality of the available evidence. Indeed, the current draft gives the impression that all foods whether listed or not in Annex IIIa could trigger allergies in a similar way and should be managed as well in a similar way from a regulatory perspective. It should be noted that only those food products which are deemed to cause intolerances or allergies based on sufficient sound data and prevalence studies are included in Annex IIIa (now Annex II of Regulation 1169/2011) and therefore subject to labelling. The recently published meta-analysis on the prevalence of fo od allergy in Europe by Nwaru et al (2014) (admittedly not available for the original draft) is worthy of consideration.
6. Epidemiology of food allergy	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
6. Epidemiology of food allergy	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals?

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
6. Epidemiology of food allergy	FoodDrinkEurope	6.1 Methodological considerations (Lines 1074-1112) and 6.2 Prevalence (lines 1113-1130) The epidemiology of food allergy is described cursorily and the conclusions do not readily provide the reader with a clear picture of the public health impact of food allergy. The final estimates contrast with the review and meta-analysis recently published by Nwaru et al (2014), admittedly not available to the Panel, conducted during approximately the same period of time (started early 2012). More information would be welcome over prevalence in any country and prevalence in Europe (which is essential to understanding the public health impact within the EU).
6. Epidemiology of food allergy	FoodDrinkEurope	6.4. Severe reactions/anaphylaxis (lines 1147-1165) Severe reactions and anaphylaxis are the principal adverse outcomes which allergy and allergen management aim to avoid, and are critical drivers for the poor quality of life experienced by many people with food allergies. The following relevant sources are communicated in order to be taken into consideration (e.g. CICBAA, the German anaphylaxis register - http://www.anaphylaxie.net/) from which publications have emanated e.g. Hompes et al (2011)*. Indeed, it is difficult to credit that there are not additional publications more recent than 2008. *Hompes S, Köhli A, Nemat K, Scherer K, Lange L, Rueff F, Rietschel E, Reese T, Szepfalusi Z, Schwerk N, Beyer K, Hawranek T, Niggemann B, Worm M. Provoking allergens and treatment of anaphylaxis in children and adolescents – data from the anaphylaxis registry of German-speaking countries. Pediatr Allergy Immunol 2011; 22: 568–574.
6. Epidemiology of food allergy	FoodDrinkEurope	6.5 Prevalence of allergy to foods not listed in Annex IIIa (lines 1166 – 1262) The view on allergenic foods not included in Annex IIIa/Annex II is unclear. The rationale for inclusion of particular foods (and exclusion of others) within the scope of this section is not provided. No view appears to be taken of the public health importance of the foods discussed in this section, which is critical for decisions by risk managers. Additionally we note that whilst the influence of biogenic amines such as histamine on accurately determining prevalence rates of IgE-mediated allergy for some foods is briefly mentioned in the introduction to section 6.5, and in the section on vegetables, it is not made clear that this may also be a concern for fruits such as strawberries and tomatoes, nor is there any assessment of its impact. It would be useful if estimates of incidence were included, including data from serious adverse reaction registries mentioned previously (e.g. German Anaphylaxis registry, CICBAA, etc) to fur ther refine assessment of the public health impact of food allergy.
6. Epidemiology of food allergy	Food & Drink Federation	1.1 Methodological considerations (Lines 1074-1112) and 1.2 Prevalence (lines 1113-1130) The description of the epidemiology of food allergy is cursory and the conclusions provided do not readily give a clear picture of the public health impact of food allergy. The final estimates are not in line with the review and meta-analysis recently published by Nwaru et al (2014), conducted during approximately the same period of time.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Further information on prevalence by country and prevalence in Europe would be beneficial, as it is essential to understanding the public health impact within the EU. 6.5 Prevalence of allergy to foods not listed in Annex IIIa (lines 1166 – 1262) The Panel's view on allergenic foods not included in Annex IIIa/Annex II is unclear and the rationale for the inclusion of particular foods (and exclusion of others) within the scope of this section is not provided. Views on the public health importance of the foods discussed in this section are unclear, which is unfortunate, given t hat they are critical for decisions by risk managers. Furthermore, it would be useful if estimates of incidence were included, to further refine assessment of the public health impact of food allergy.
6. Epidemiology of food allergy	nutrition counselling	Lines 1073 ff: Two European meta-analyses provide data for epidemiology and prevalence of food allergy in Europe (1, 2) 1. Nwaru BI, Hickstein L, Panesar SS, Muraro A, Werfel T, Cardona V, et al. The epidemiology of food allergy in Europe: a systematic review and meta-analysis. Allergy. 2014;69(1):62-75. 2. Nwaru BI, Hickstein L, Panesar SS, Roberts G, Muraro A, Sheikh A. Prevalence of common food allergies in Europe: a systematic review and meta-analysis. Allergy. 2014;69(8):992-1007.
6. Epidemiology of food allergy	The iFAAM FP7 Project	A major meta analysis of allergy prevalence data (Nwaru et al Allergy 2014 69 62-75) should be considered.. A distinction between data drawn from unselected populations using rigorous diagnostic procedures (e.g. DBPCFC) and those drawn from outpatient clinic subjects (most often diagnosed from patient history) should be made. The lack of this distinction results in a lack of clarity regarding data presented in the Opinion. In particular, key outputs from the Nwaru study (e.g. self-reported allergy in children and adults vs challenge positive prevalence) should be included. . Only one of the previous studies examined the time trends in the frequency of food allergy and concluded that it is unclear whether the prevalence is increasing. The observed increase over time could be attributed to increased awareness and improved pattern of reporting and diagnosis rather than a true increase respectively. The Nwaru study did specifically consider the European perspective and concluded that the frequency of IgE-media ted food allergy is higher among children than among adults and highest in North Western Europe than in other regions, while Southern Europe seems to have the lowest prevalence, although a lack of studies in the South of Europe was noted. Severe reactions and anaphylaxis are the principal adverse outcomes which allergy and allergen management aim to avoid, and are critical drivers for the poor quality of life experienced by many people with food allergies. This section should be elaborated to include other relevant sources that are currently missing (e.g. CICBAA, the German anaphylaxis register Hompes et al Pediatr Allergy Immunol 2011; 22: 568–574. (2011). No view appears to have been taken of the public health importance of the foods discussed in this section, which is critical for decisions by risk managers. Additionally, we note that whilst the influence of biogenic amines such as histamine on accurately determining prevalence rates of IgE-mediated allergy for some foods is briefly mentioned in th e introduction to

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		section 6.5, and in the section on vegetables, it is not made clear that this may also be a concern for fruits such as strawberries and tomatoes, nor is there any assessment of its impact.
7. Influence of environmental and individual factors in the distribution of food allergies	EAACI	This section is not balanced in its presentation of the current state of knowledge with some factors such as food processing, the hygiene hypothesis and microbial exposure being treated in a superficial manner and not reflecting the large body of literature now available with regards the latter. The part on of genetics (paragraph 7.2.1, line 1362-173) totally fails mention the filaggrin mutation and its possible impact on risk of food allergy. Nwaru et al (Allergy 2014 69 62-75) in their meta-analysis considered risk factors but found the evidence base inconclusive and inconsistent. The lack of conclusive factors relates to the quality of prevalence data in general (see section 6). Amongst other factors sex, age, country of residence, the presence of other allergic diseases, and familial history of allergy may all be important. The EFSA opinion considers food consumption patterns in relation to food allergy incidence. However, without a good quality evidence base it is difficult to judge its role. Comments ar e made (e.g. line 1291) that proteins are more likely to be allergenic when abundant in a food. This is a hypothesis and not proven. There are food allergens which are not major components; for example certain Bet v 1 homologues and LTP allergens can be minor components in some food such as apple and yet important food allergens. Feeding practices early in life and breastfeeding are discussed this makes no mention of the studies on going across the world that will deliver important new data on the early introduction of allergenic foods into the diets of infants and young children such as the UK-funded EAT and LEAP studies and the German funded PEAD and HEAP studies. The academy would welcome discussion of the conclusion of the EAACI Food Allergy Guidelines group in this regard in any revision of the Opinion. The guidelines concluded that all mothers can consume a normal diet without restrictions during pregnancy and lactation and that for all infants, exclusive breastfeeding is recommended for at least first 4-6 months of life. If breastfeeding is insufficient or not possible, infants at high-risk of developing a food allergy can be recommended a hypoallergenic formula with a documented preventive effect for the first 4 months. There is no need to avoid introducing complementary foods beyond 4 months, and currently, the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months (c.f. Muraro et al Allergy. 2014 69(5):590-601). Cnce weaning has commenced, irrespective of atopic heredity. There is no evidence to support the use of prebiotics or probiotics for food allergy prevention.
7. Influence of environmental and individual factors in the distribution of food allergies	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
7. Influence of environmental and individual factors in the distribution of food allergies	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
7. Influence of environmental and individual factors in the distribution of food allergies	FoodDrinkEurope	7 – Influence of environmental and individuals factors in the distribution of food allergies (lines 1271-1424) Some factors (e.g. genetic background, age and sex) are discussed at some length, while others (e.g. food processing, hygiene hypothesis, microbial exposure) are discussed less, despite the rather large number of publications and the importance of the postulated influences. It is also notable that different routes of exposure and potential sensitisation to food proteins, such as inhalation and /or skin contact (and the currently postulated Dual Exposure Hypothesis (Lack 2012*), are not discussed in this section. Subsection 7.2.5 – Other individual factors seem to be more relevant to the reactions on exposure, except for the gastric acidity inhibitors. The conclusion is also rather limited, but the statement concerning prevalence is very pertinent. * Lack G. Update on risk factors for food allergy. J Allergy Clin Immunol 2012;129(5):1187-97
7. Influence of environmental and individual factors in the distribution of food allergies	Food & Drink Federation	(lines 1271-1424) Some factors (e.g. age and sex) are discussed in detail in the Opinion, while others (e.g. food processing, hygiene hypothesis, microbial exposure) are given less coverage, despite the large number of publications and the importance of the postulated influences. We would also question why different routes of exposure and potential sensitisation to food proteins, such as inhalation and/or skin, are not discussed in this section. Subsection 7.2.5 – Other individual factors - seems to be more relevant to the reactions on exposure, except for the gastric acidity inhibitors. The conclusion is also rather limited, but the statement concerning prevalence is very pertinent.
7. Influence of environmental and individual factors in the distribution of food allergies	The iFAAM FP7 Project	Nwaru et al (Allergy 2014 69 62-75) in their meta-analysis considered risk factors but found the evidence base inconclusive and inconsistent. Amongst other sex, age, country of residence, the presence of other allergic diseases, and familial history of allergy may all be important. The lack of conclusive factors relates to the quality of prevalence data in general (see section 6). It is also notable that different routes of exposure and potential sensitisation to food proteins, such as inhalation and /or skin contact (and the currently postulated Dual Exposure Hypothesis (Lack J Allergy Clin Immunol 2012;129(5):1187-97), are not discussed in this section. No reference is made to the role of filaggrin mutations as a risk factor for developing allergic disease. Subsection 7.2.5 – Other individual factors seems to be more relevant to the reactions on exposure, except for the gastric acidity inhibitors. The conclusion is also rather limited, but the statement concerning prevalence is very

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		pertinent. There is a need to improve this evidence base in order to validly estimate the putative frequency of food allergy. The EFSA Opinion considers food consumption patterns in relation to food allergy incidence. However, without a good quality evidence base it is difficult to judge its role. Comments are made (e.g. line 1291) that proteins are more likely to be allergenic when abundant in a food. This is a hypothesis and not proven. There are food allergens which are not major components – for example certain Bet v 1 homologues; LTP allergens can be minor components in some foods such as apple and yet important food allergens. Feeding practices early in life and breastfeeding are discussed and could allude to the conclusion of the EAACI Food Allergy Guidelines in this regard but makes no mention of the studies ongoing across the world that will deliver important new data on the early introduction of allergenic foods into the diets of infants and young children. (c.f. Muraro et al Allergy. 2014 69(5):590-601). The guidelines concluded that all mothers can consume a normal diet without restrictions during pregnancy and lactation and that for all infants, exclusive breastfeeding is recommended for at least first 4-6 months of life. If breastfeeding is insufficient or not possible, infants at high-risk of developing a food allergy can be recommended a hypoallergenic formula with a documented preventive effect for the first 4 months. There is no need to avoid introducing complementary foods beyond 4 months, and currently, the evidence does not justify recommendations about either withholding or encouraging exposure to potentially allergenic foods after 4 months once weaning has commenced, irrespective of atopic heredity. There is no evidence to support the use of prebiotics or probiotics for food allergy prevention.
8. Characterisation of food allergens	EAACI	In general this aspect of the opinion is well written. However the section covered by lines 1665-1676 contains several factual errors and omissions. For example it is stated that LTP allergens are responsible for most reactions to Rosaceae fruit. This is incorrect as the majority are related to sensitisation to the pollen allergen Bet v 1. Instead LTP allergens are responsible for the majority of severe reactions. The sections on mass spectrometry are incomplete and confused. For examples, the description of intact mass determination and peptide mass fingerprinting is muddled. A protein mass fingerprint is not obtained from an intact protein except in unusual circumstances which have not been applied to allergens. In addition, 'gas-phase ionisation' suggests the intact protein is in the gas phase at the point of ionisation which is not correct and does not relate to the ionisation method in any case. Lastly, the statement "Tandem mass spectrometry (MS/MS), in the most commonly performed ―bottom-up direction, allows sequencing on proteolytic peptides obtained by previous digestion with enzymes." is largely incorrect. Identification of peptides using MS2 data is almost always performed by comparison with a suitable translated DNA sequence set and not through de novo sequencing as is implied.
8. Characterisation of food allergens	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
8. Characterisation of food allergens	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
8. Characterisation of food allergens	FoodDrinkEurope	8 - Characterisation of food allergens (lines 1425-1743) The subsection on immunological characterisation would benefit from analysis of functional immunological characterisation. It does make the pertinent and important point that immunological characterisation only provides information about antigenicity, not allergenicity (although the use of functional assays might partially address this issue). We also note that no mention is given to potential need to consider the role of components other than protein, such as lipids (Bublin et al 2014**) in determining the allergenic potential of allergenic food. ** Bublin M, Eiwegger T, Breiteneder H.2014. Do lipids influence the allergic sensitization process? J Allergy Clin Immunol. 2014 May 28. pii: S0091-6749(14)00590-9. doi: 10.1016/j.jaci.2014.04.015. [Epub ahead of print] This section refers to PDB datafiles as "Program database files": is it an acronym for "Protein Databank files"? It is stated that LTPs are responsible for most of the reactions to fruit s of the Rosaceae family while by far it is pollen cross-reactivity related to PR proteins. We suggest that the statement should be qualified by adding "severe".
8. Characterisation of food allergens	Food & Drink Federation	(Line 1465) This section refers to PDB datafiles as "Program database files": We would question whether this is an acronym for "Protein Databank files"? (Lines 1526-1529) We would suggest that the statement that 'LTPs are responsible for most of the reactions to fruits of the Rosaceae family' be qualified by adding the word "severe". (lines 1728-1743) The subsection on immunological characterisation would benefit from analysis of functional immunological characterisation. It does make the important point that immunological characterisation only provides information about antigenicity, not

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		allergenicity. We also note that no mention is given to the potential need to consider the role of components other than protein, such as lipids (Bublin et al 2014**) in determining the allergenic potential of allergenic food. ** Bublin M, Eiwegger T, Breiteneder H.2014. Do lipids influence the allergic sensitization process? J Allergy Clin Immunol. 2014 May 28. pii: S0091-6749(14)00590-9. doi: 10.1016/j.jaci.2 014.04.015. [Epub ahead of print]
8. Characterisation of food allergens	Interassociation des personnes allergiques et intolérantes	Report readers might benefit of EFSA panel scientific expertise about validation of dosage methods prior to new recipe production (matrix effect) and routine check. An analytical result only based on kit application without real validation is of no use. Normalization is on the way but seems out of the general threshold discussion for the moment. Could Efsa expert provide their opinion on this Normalization ?
8. Characterisation of food allergens	nutrition counselling	Lines 1527-1529: In northern Europe Bet v 1, not LTP, is mainly responsible for allergic reactions to fruits from Rosaceae.
8. Characterisation of food allergens	The iFAAM FP7 Project	The section covered by lines 1665-1676 contains several factual errors and omissions. Firstly, there are many more types of ionisation used in mass spectrometry than electrospray (ESI) and matrix assisted laser desorption ionisation (MALDI), although these are frequently used for the study of proteins. Secondly, the description of intact mass determination and peptide mass fingerprinting is confused. A protein mass fingerprint is not obtained from an intact protein except in unusual circumstances which have not been applied to allergens. In addition, 'gas-phase ionisation' suggests the intact protein is in the gas phase at the point of ionisation which is not correct and does not relate to the ionisation method in any case. Thirdly the statement "Tandem mass spectrometry (MS/MS), in the most commonly performed ―bottom-up direction, allows sequencing on proteolytic peptides obtained by previous digestion with enzymes." is largely incorrect. Identification of peptides using MS2 data is almost always performed by comparison with a suitable translated DNA sequence set and not through de novo sequencing as is implied. The section does not mention functional immunological characterisation. It does make the pertinent and important point that immunological characterisation only provides information about antigenicity, not allergenicity (although the use of functional assays might partially address this issue). We also note that no mention is given to the potential need to consider the role of components other than protein, such as lipids (Bublin et al J Allergy Clin Immunol. 2014 doi: 10.1016/j.jaci.2014.04.0152014) in determining the allergenic potential of allergenic food. No mention is made in section 8.3.2 about the role of alpha-galactose in allergies to meat. The section refers to PDB data files as "Program database files" but if these are referring to protein structure files the acronym is "Protein Databank files"?
8. Characterisation of food allergens	Università del Piemonte Orientale A. Avogadro, Italy (Institution ex art 36 recognised by EFSA)	PLEASE NOTE THAT: Par. 8.3.1 The presented are certainly the 4 main allergenic protein superfamilies, but many other relevant allergens have been left aside (e.g. chitinases, responsible of the kiwi-latex syndrome) Par 8.3.2 Several other allergenic proteins are missing, above all ovalbumins, ovomucoids and transferrins, main responsible of bird allergy syndrome
9. Cross-reactivities	EAACI	The phrasing of this section is unclear and could be misleading and cause confusion. As mentioned in the earlier overall comments no mention is made of alpha-galactose and allergy to meat.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
9. Cross-reactivities	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	Special case of rapeseed protein: in early February we have been informed about the forthcoming authorisation of rapeseed protein as a novel food. The draft Commission Implementing Decision contained a special labelling provision according to which "any foodstuff containing rapeseed protein shall bear an easily visible and legible statement that the product containing 'rapeseed protein' as a food ingredient may cause allergic reaction to consumers who are allergic to mustard and products thereof". The proposal of labelling products containing rapeseed protein in a way that it is made clear that they can provoke cross reaction in people allergic to mustard is NOT acceptable. Either rapeseed protein is considered as an allergen that has to be listed in future Annex II of Regulation on Food Information to Consumers (which will enter into force as for December 2014), and therefore products containing this protein have to follow the same labelling requirements as those containing the other 14 existing allergen, o r it is not an allergen. If this is the approach that has been suggested by EFSA (the Agency is responsible for updating the list of allergen in the EU), then products containing rapeseed protein should NOT present any label on the fact that this may provoke cross reaction in people allergic to mustard. Cross reactions happens with other foods too, such as almonds and peach seeds. We do not label green peas, green beans or lentils, even if peanut allergic people might cross-react. Information about possible cross reaction is best handled as a patient education issue. If people with mustard allergy are at risk, then they should learn to avoid this protein. It should be the task of the dietitian or doctor to give the information on possible cross reaction to the person allergic to mustard. Unfortunately, many patients do not get educated on this topic, so better patient education is of course needed, but it is NOT helpful to label products for cross reaction when there are so many different individual reactions.
9. Cross-reactivities	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
9. Cross-reactivities	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac'

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG'

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
9. Cross-reactivities	FoodDrinkEurope	9 – Cross-reactivities (lines 1744-1789) Line 1765: The phrasing "pollen allergens cross-react with LTP" is confusing; clearly there will be cross-reactivity if the LTPs are present, but this is not how it comes across The cross-reactivity between mammalian meats due to Galactose-alpha-1,3-galactose should be taken into consideration. The overall conclusion does not really address the magnitude of the public health impact or where attention would need to be focussed to address it.
9. Cross-reactivities	Food & Drink Federation	(Line 1765) The phrasing "pollen allergens cross-react with LTP" is confusing. There will be cross-reactivity if the LTPs are present, but this is overstated. The cross-reactivity between mammalian meats due to Galactose-alpha-1,3-galactose should be taken into consideration. (Lines 1790-1795) The overall conclusion does not really address the significance of the public health impact or where attention would need to be focussed to address it.
10. Effects of food processing on allergenicity	EAACI	This section is inconsistent; it would benefit from cross-referencing effectively with the food-by-food sections included further on the document. There are many omissions. For example, the effects of deamidation of gluten in inducing the formation of potent peptides capable of eliciting severe reactions is not included (Denery-Papini S, Bodinier M, Larré C, Brossard C, Pineau F, Triballeau S, Pietri M, Battais F, Mothes T, Paty E, Moneret-Vautrin DA. Allergy. 2012 Aug;67(8):1023-32.).
10. Effects of food processing on allergenicity	FEDIOL	A good example of the way processing can affect the allergenicity of foods is explained in EFSA opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from FEDIOL and IMACE on fully refined soybean oil and fat pursuant to Article 6, paragraph 11 of Directive 2000/13/EC- for permanent exemption from labelling, as adopted on 15 October 2007. The opinion states that with the process by which soybean oils are neutralised (alkali refined) bleached and deodorised (N/RBD), it is not very likely that such N/RBD soybean oils will trigger a severe allergic reaction in susceptible individuals under the conditions of production and use. This analysis, together with the supporting clinical data, led to the permanent exemption from "allergen" labelling under Directive 2003/13 and under Regulation 1169/2011 of fully refined soybean oil

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		and fat and products thereof, "insofar as the process that they have undergone is not likely to increase the level of allergenicity assessed by EFSA for the relevant product from which they originated". Another good example is the evaluation of tocopherols from soya under the same procedure. The EFSA opinion in this case was "Considering the information provided by the applicant regarding the starting material, the subsequent production process, and the demonstration of low residual protein content, the Panel considers that it is unlikely that natural mixed tocopherol/D-alpha tocopherols from soybean sources will trigger a severe allergic reaction in susceptible individuals." (Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from Cognis, ADM and Cargill on natural mixed tocopherols (E306), natural D-alpha tocopherol, natural D-alpha tocopherol acetate and natural D-alpha tocopherol succinate from soybean sources pursuant to Article 6, paragraph 11 of Directive 2000/13/EC, as adopted on 3 May 2007). These are excellent illustrations of the situation where processing reduces the protein content of the original allergenic source to such an extent that the amount remaining poses a negligible risk, and thereby also underlines the power of quantitative risk assessment, as well as its feasibility.
10. Effects of food processing on allergenicity	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
10. Effects of food processing on allergenicity	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways'

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define “high temperature” for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – “Almonds are not nuts…” a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo ‘DBPCFC’ not ‘DBPCFG’ • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
10. Effects of food processing on allergenicity	FoodDrinkEurope	10 – Effects of food processing on allergenicity (lines 1796-1948) We would like to note that some significant findings are missing. It would also be useful to cross-reference 7.1.2 to this section. Specific comments include: - It should be clarified if allergenicity in introductory paragraph refers to allergenic sensitising potency or to the potential to trigger reactions - line 1821: with regards to the phrase within the brackets: "eventually reversible", does this phrase meant to be: eventually irreversible? - The following more recent publication should be taken into consideration Thomas et al (2006) - In relation to hydrolysis, there is no mention of animal and human studies that have been undertaken to determine residual reactivity, for example Van Hoeyveld et al 1998 and Terheggen-Lagro et al 2002***, nor of the American Academy of Pediatrics de facto standard for acceptance of a formula as hypoallergenic – this might raise some questions on determination of safety. - The work on Cor a1 is cit ed in terms of IgE binding effects, but the (admittedly limited) work in allergic individuals is not mentioned, even though it provides one example of investigating the clinical consequences of an observed reduction in IgE binding (Skamstrup Hansen et al 2003). - No mention of protein isolates, deamidation and altered allergenic sensitising potential ***Terheggen-Lagro, S.W., Khouw, I.M., Scahaafsma, A., Wauters, E.A., 2002. Safety of a new extensively hydrolysed formula in children with cow's milk protein allergy: a double blind crossover study. BMC Paediatrics 2 Van Hoeyveld, E.M., Escalona-Monge, M., De Swert, L.F.A., Stevens, E.A.M., 1998. Allergenic and antigenic activity of peptide fragments in a whey hydrolysate formula. Clinical and Experimental Allergy 28, 1131-1137. American Academy of Pediatrics (2000) Hypoallergenic infant formulas, Pediatrics 106(2), 346-349.
10. Effects of food processing on allergenicity	Food & Drink Federation	(lines 1796-1948) We would suggest that some significant findings are missing. It would also be useful to cross-reference 7.1.2 to this section. Specific comments include: - It should be clarified whether allergenicity in the introductory paragraph refers to allergenic sensitising potency or to the potential to trigger reactions - line 1821: should the phrase within the brackets: 'eventually reversible' read 'eventually irreversible'? - The more recent publication by Thomas et al (2006) should be taken into consideration. In relation to hydrolysis, there is no mention of animal and human studies that have been undertaken to determine residual reactivity, for example Van Hoeyveld et al 1998 and Terheggen-Lagro et al 2002***, nor of the American Academy of Pediatrics de facto standard for acceptance of a formula as hypoallergenic. - The work on Cor a1 is cited in terms of IgE binding effects. However, the work in allergic individuals is not mentioned ,

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		even though it provides one example of investigatin g the clinical consequences of an observed reduction in IgE binding (Skamstrup Hansen et al 2003). - There is no mention of protein isolates, deamidation and altered allergenic sensitising potential ***Terheggen-Lagro, S.W., Khouw, I.M., Scahaafsma, A., Wauters, E.A., 2002. Safety of a new extensively hydrolysed formula in children with cow's milk protein allergy: a double blind crossover study. BMC Paediatrics 2 Van Hoeyveld, E.M., Escalona-Monge, M., De Swert, L.F.A., Stevens, E.A.M., 1998. Allergenic and antigenic activity of peptide fragments in a whey hydrolysate formula. Clinical and Experimental Allergy 28, 1131-1137.
10. Effects of food processing on allergenicity	R-Biopharm AG	1860ff Please also consider a paper of Gessendorfer et al. (Gessendorfer, B.; Koehler, P. & Wieser, H. Preparation and characterization of enzymatically hydrolyzed prolamins from wheat, rye, and barley as references for the immunochemical quantitation of partially hydrolyzed gluten. Anal Bioanal Chem, 2009, 395, 1721-1728
10. Effects of food processing on allergenicity	The iFAAM FP7 Project	This section would benefit from cross-referencing effectively with section 7.1.2 and to the food-by-food sections included further on the document. It provides on generalisations and does not contribute to a thorough assessment of the public health impact of changes induced by processing. Some significant findings are missing: - Is allergenicity in the introductory paragraph referring to allergenic sensitising potency or to the potential to trigger reactions? This needs to be clarified. - line 1821: eventually irreversible? - More recent reviews than Davis and Williams (1998) exist e.g. Thomas et al (2006) - In relation to hydrolysis, there is no mention of animal and human studies that have been undertaken to determine residual reactivity, for example Van Hoeyveld et al 1998 and Terheggen-Lagro et al 2002***, nor of the American Academy of Pediatrics de facto standard for acceptance of a formula as hypoallergenic – this might raise some questions on determination of safety. - The work on Cor a1 is cite d in terms of IgE binding effects, but the (admittedly limited) work in allergic individuals is not mentioned at all, even though it provides one example of investigating the clinical consequences of an observed reduction in IgE binding (Skamstrup Hansen et al 2003). - No mention of protein isolates, deamidation and altered allergenic sensitising potential; this is despite the fact acid hydrolysed gluten has been shown to be an extraordinarily potent allergen in individuals otherwise able to consume gluten and resulted in severe reactions and product recall. ***Terheggen-Lagro, S.W., Khouw, I.M., Scahaafsma, A., Wauters, E.A., 2002. Safety of a new extensively hydrolysed formula in children with cow's milk protein allergy: a double blind crossover study. BMC Paediatrics 2 Van Hoeyveld, E.M., Escalona-Monge, M., De Swert, L.F.A., Stevens, E.A.M., 1998. Allergenic and antigenic activity of peptide fragments in a whey hydrolysate formula. Clinical and Experimental Allergy 28, 1131-1137.
10. Effects of food processing on allergenicity	Università del Piemonte Orientale A. Avogadro, Italy (Institution ex art 36 recognised by EFSA)	- Suggestion 1: please note that, among the “food processing”, the extraction effect (e.g. cold pressed oil extraction; extraction of oil from seeds/fruits using organic solvents…) is completely missed in this section, despite some data regarding this point are reported in some specific section (e.g. hazelnut allergens section). We suggest inserting some sentences here, like:

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Extraction of oil and lipid material from matrices and residual presence of hidden allergens is largely affected by processing parameters, solvent capacity and food matrix nature. Few data reports focused deep investigation about this point. Moreover, some works highlight the potential residual presence of allergenic proteins depending on the nature of the extraction, like in the case of hazelnut oil. The adulteration of extra virgin olive oil with solvent-extracted hazelnut oil can be traced by a simple SDS-PAGE analysis, and that adulteration introduces a potential risk for hazelnut allergic patients. (Ref. Food Addit Contam Part A Chem Anal Control Expo Risk Assess. 2010 Jan;27(1):11-8. doi: 10.1080/02652030903225799. Olive oil adulterated with hazelnut oils: simulation to identify possible risks to allergic consumers. Arlorio M, Coisson JD, Bordiga M, Travaglia F, Garino C, Zuidmeer L, Van Ree R, Giuffrida MG, Conti A, Martelli A. - Suggestion 2: following the Line 1938 (or in the specific session "10.6 Multiple treatments") we suggest to insert: The combined serial employment of non-thermal and thermal techniques based on ultrasounds and microwaves was investigated. Incubation with specific anti-Pru p 3 serum showed how treating peach peel with microwave at 140 °C and with ultrasound does not eliminate Pru p 3 IgE binding properties. Also in this case, the application of MW/US protocol on peach pulp appeared to be insufficient for the reduction of IgE binding capacity to Pru p 3. (Ref: J Agric Food Chem. 2012 5;60(35):8755-62. Evaluation of the impact of sequential microwave/ultrasound processing on the IgE binding propert ies of Pru p 3 in treated peach juice. Garino C, Zitelli F, Travaglia F, Coisson JD, Cravotto G, Arlorio M. - Ultrasound-microwave Assisted Extraction has been recently described in order to extract and eliminate allergens from castor bean (Ricinus communis) bean meal, with interesting results, showing the potential of this under-investigated approach. (Advanced Materials Research, Vols 781-784 (2013) pp 721-725. Ultrasound-Microwave Assisted Extraction and separation of Ricinus communis Allrgen from castor bean meal. Ailin Zhang, Changlu Wang, Yufeng Hu, Zhijiang Zhou) - Other novel techniques, like atmospheric/cold plasma (among the different examples of Non Thermal Plasma Treatments, NTPT), particularly concerning the thin layer treatment of liquid foods, were not deeply investigated, until today.
11. Methods for the detection of allergens and allergenic ingredients in food	Bioseutica B.V.	Dear Sirs In our opinion, a consistent approach should be followed for all substances known, contained and deliberately added to wine. If for sulphites the absence of clear scientific data is enough to remain with a very high limit for labelling of more than 10 ppm (10 mg/kg or 10 mg/L) is sufficient, despite the availability of more sensitive assays (as pointed out in the conclusions from the EFSA Panel on Dietetic Products, Nutrition and Allergies), then the same practical approach should be also followed for other potential allergens such as Lysozyme. The NDA Panel stated clearly that the current ELISA method used for lysozyme detection is unreliable and unreproducible, and this is due to the biochemical nature and inherent variation of the components of such immunological kit (antibody

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		source stability-specificity, extraction buffer matrix effect, etc.,). As a major supplier of Lysozyme for the food industry, Bioseutica can confirm the statements with respect to the immunological assays based on its own in-house data. However, similar to the sulphites' case, there are relatively cheap and robust analytical methods available for detecting lysozyme with detection limits of 5-10 ppm. Bioseutica would therefore request EFSA to consider one of those methods - HPLC or the microbiological testing method inhibition zone testing on agar plates- as the analytical method of choice to establish the LoD (Limit of Detection) of lysozyme in wine. In addition, Bioseutica wants to point out that allergenicity to egg white components is more common among infants than adults, and most children will outgrow it by the age of five. Egg white contains several proteins of which lysozyme is only one minor component [3.4% of the total egg white proteins]. Most people who are allergic to hen's eggs have antibodies which react to one of the following four proteins in the egg white: ovomucoid (11% of the total egg white proteins), ovalbumin (54% of the total egg white proteins), ovotransferrin (12% of the total egg white proteins), and lysozyme; among them ovomucoid , is the most common target of the immune system attack. For this reason, the use of Lysozyme has to be declared according to the allergen labelling instructions of EU (EC 2003, Council Directive 2003/89). As the allergenicity risk and concern is basically associated with infants, it seems not totally logic to apply the strictest/ impractical labelling criteria to Lysozyme when used as processing aid/ additive in alcoholic beverages, including wine, which are intended for adult population only.
11. Methods for the detection of allergens and allergenic ingredients in food	EAACI	This section (specifically lines 2135-2163) compounds the errors in section 8 (lines 1665-1676). Additionally the list of instruments 'able to perform MS/MS' omits commonly used devices such as orbital ion traps. Regarding different detection methodologies (lines 1950-1974), the distinction between methods capable of detecting the chemical entity which causes the risk (i.e. protein allergens) and those which use the presence of a (generally coincident) molecule (i.e. DNA) is crucial. This is important to address since this was part of the original request from the FSAI. As is noted elsewhere, different processing may affect the relative recovery of DNA and protein allergens which could cause potential false negative or positive results. Also the Table included in this section does not distinguish between methods used for research purposes and those used for analysis for regulatory enforcement, a distinction which would be extremely helpful to those unfamiliar with analytical methodology. Regarding the quantif ication of allergens by mass spectrometry (lines 2164-2184), C12 light isotope tagged peptides are not generally used for quantitation of allergens but rather 13C/15N peptides are used. It should be noted that quantitative MS detects molar amount of peptide which must then be converted to a mass of protein and/or foodstuff. Also, in this section, as well as in others, examples of limit of detection (LoD) and limit of quantification values are stated (e.g. 1 and 4 mg/L) without reference to what the units are (e.g. mg/L protein/peptide/foodstuff). Without this information the LoD values referenced are essentially meaningless. The opinion is consistent with the food allergy guidelines (Muraro et al Allergy. 2014 doi: 10.1111/all.12453.) where it was also identified that the lack of reference materials (RM) and certified reference materials (CRM) is a significant issue for the allergen community. The meaning of the terms RM and CRM in the context of this report should be defined. We suggest ISO guide 30 as a t erm of reference in this regard. We are unaware of the existence of a peanut CRM which fulfils the criteria of ISO guide 30 (e.g. metrological traceability). New data have appeared in the literature comparing the performance

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		of allergen immunoassay (Johnson et al A multi-laboratory evaluation of a clinically-validated incurred quality control material for analysis of allergens in food. Food Chem. 2014 Apr 1;148:30-6) which maybe useful to include in any revision of the Opinion.
11. Methods for the detection of allergens and allergenic ingredients in food	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	EFSA should pay attention to the methods and the normalisation process. In particular, the "proprietary methods" will not give all the information for lab users and thus, it might drive to wrong conclusion of the test. What is more, there is a need to officially specify the relevant method of analysis for detecting each allergen. Currently the use of methods for the detection of allergens varies from actor to actor: authorities responsible for checking allergens might use certain methods, while private labs use the others. Variety of used methods increases the risk of getting different results, thus if methods are clearly defined and processed this risk is avoided and consumers feel more protected. Moreover, this could serve as a real basis for starting future discussions on allergens thresholds.
11. Methods for the detection of allergens and allergenic ingredients in food	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
11. Methods for the detection of allergens and allergenic ingredients in food	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
11. Methods for the detection of allergens	FoodDrinkEurope	11 – Methods for the detection of allergens and allergenic ingredients in food (lines 1949-2196) While the section discusses the fact that DNA methods do not measure the amount of protein present, it does not elaborate on

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
and allergenic ingredients in food		the possibility of false negatives (not enough DNA), false positives (similar species, improper primers) and how the results can be used in risk assessment. Further elaboration is also required on the reference materials referred to in section 11.2.4, line 2305 as this suggests there are certified reference materials available for allergenic food stuffs - as these have been used for DNA equivalence studies – but this is at odds with highlighted lack of certified reference materials repeatedly mentioned elsewhere in section 11. Section 11 also does not discuss the context in which analytical methods should be applied. Analytical results are only useful if the samples analysed have been taken as part of a correctly designed study, with a clearly defined aim, so that the sampling procedures and subsequent analyses are correctly designed/selected and implemented. Along the same lines, it does not discuss how different techniques can be used in a complementary manner. Specific comments: - In principle, a quantitative method is only required where quantitative risk assessment will follow. Where zero tolerance is applied, only a qualitative yes/no answer is required. - Certified Reference Materials are indeed important but there is a lot that can be done without them. CRMs should not be confused with standards. - Some particularly pertinent references are not cited e.g. Johnson PE et al (2014)(but available online 29 September 2013, which reports a ring trial using 2 different allergenic foods and several different kits. - The section does not comment on the application of analytical methods under various circumstances, nor how they can be used in developing or validating risk assessments. Phil E. Johnson, Neil M. Rigby, Jack R. Dainty, Alan R. Mackie, Ulrike U. Immer, Adrian Rogers,Pauline T itchener, Masahiro Shoji, Anne Ryan, Luis Mata, Helen Brown, Thomas Holzhauser,Valery Dumont, Jill A. Wykes, Michael Walker, Jon Griffin, Jane White, Glenn Taylor,Bert Popping, René Crevel, Sonia Miguel, Petra Lutter, Ferdelie Gaskin, Terry B. Koerner,Dean Clarke, Robin Sherlock, Andrew Flanagan, Chun-Han Chan, E.N. Clare Mills. Food Chemistry 148 (2014) 30–36. A multi-laboratory evaluation of a clinically-validated incurred quality control material for analysis of allergens in food.
11. Methods for the detection of allergens and allergenic ingredients in food	FoodDrinkEurope	• 46/2002 –ELISA's cannot be regarded as fully 'qualitative' given issues with calibrants / antibodies etc. • 46/ 2008 – The section would benefit from a reference to any validation required by user prior to use for kit or any matrix validation and by considering the uncertainty of measurement for biological assays which can be significant. The expression of results 0.07mg/kg for an ELISA (2011) is unrealistic when analysing real samples. • 46/2017 – No mention of analytical approaches to elucidate false positives i.e. robust matrix validation (re. analytical annex in FoodDrinkEurope guidelines on allergen management) • 47/ 2024- 2026 CRMs – "Reference materials are commercially available from different producers for most major allergens but results may not be comparable". Further explanation is needed to justify why CRMs are not comparable. • 47/2023 – Overlook work undertaken at a member-state level to approve test methodology ISO / DIN standards

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• 47/ 2028-2030 – many of the CRM's cited are not clinically relevant or have not been certified specifically for allergen testing – issues with milk CRM irradiated and proven to be highly lactosylated • 47 / 2037 – "LFDs can be semi-quantitative"; there is no discussion of the limitations associated with these assays as is highlighted for the ELISA section (e.g. matrix interference inter and intra assay variations, batch to batch variation). Additionally no mention that they require any validation. • 48 / 2081 The influence of the different calibrators used should be reported. • 49/ 2127 LCMS/MS is cited as being fit for purpose for quantification of allergen whereas its currently just quantification of peptide fragments and difficult to correlate back to the amount of allergenic protein – most of the work undertaken with MS is based on spiked not incurred materials • 50/2178 Overlooks the issues of effectiveness of tryptic digest in accurate analysis of samples • 50 / 2186-2188 quantification is not possible because of lack of refere nce materials, but not for ELISA – when results can be expressed as mg food/kg • 50 / 2197 – the key interferences associated with this method of analysis – inhibition metals / fats etc. should be taken into consideration. • 51 / 2239 Mention of "mitochondrial DNA" – must be pointed out that this makes the quantification impossible as amount/number of mitochondria will vary depending on cellular function. Competition is a key consideration for multiplexing PCR and must be taken into consideration • 52 / 2302-2305 Expression of results as of copy number of DNA it is not helpful to end user. This can be quantified, but better as mg food w/w –can be done through validation and is cited further in the Opinion • 53 / 2319 –the use of reductive agents in sample extraction (mercaptoethanol) for highly processed foods should be taken into consideration • 53/ 2344 – Overlooks that reliable incurred samples would still first require internationally agreed approved reference materials
11. Methods for the detection of allergens and allergenic	Food & Drink Federation	(Lines 1949-2196) This section does not elaborate on the possibility of false negatives (not enough DNA), false positives (similar species, improper primers) and how the results can be used in risk assessment. Further elaboration is also required on the reference

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
ingredients in food		materials referred to in section 11.2.4, line 2305, as this suggests there are certified reference materials available for allergenic food stuffs. This is contra to a highlighted lack of certified reference materials, repeatedly mentioned elsewhere in section 11. Section 11 also does not discuss the context in which analytical methods should be applied. Analytical results are only useful if the samples analysed have been taken as part of a correctly designed study, with a clearly defined aim, so that the sampling procedures and subsequent analyses are correctly designed/selected and implemented. In addition, it does not discuss how different techniques can be used in a complementary manner.
11. Methods for the detection of allergens and allergenic ingredients in food	Food & Drink Federation	(Lines 1949-2196) Specific comments: - In principle, a quantitative method is only required where quantitative risk assessment will follow. Where zero tolerance is applied, only a qualitative yes/no answer is required. - Certified Reference Materials are important but there is much that can be done without them. CRMs should not be confused with standards - Some particularly pertinent references are not cited e.g. Johnson PE et al (2014), which reports a ring trial using 2 different allergenic foods and several different kits. - The section does not comment on the application of analytical methods under various circumstances, nor how they can be used in developing or validating risk assessments. Phil E. Johnson, Neil M. Rigby, Jack R. Dainty, Alan R. Mackie, Ulrike U. Immer, Adrian Rogers,Pauline Titchener, Masahiro Shoji, Anne Ryan, Luis Mata, Helen Brown, Thomas Holzhauser,Valery Dumont, Jill A. Wykes, Michael Walker, Jon Griffin, Jane White, Glenn Taylor,Bert Popping, René Crevel, Sonia Miguel, Pet ra Lutter, Ferdelie Gaskin, Terry B. Koerner,Dean Clarke, Robin Sherlock, Andrew Flanagan, Chun-Han Chan, E.N. Clare Mills. Food Chemistry 148 (2014) 30–36. A multi-laboratory evaluation of a clinically-validated incurred quality control material for analysis of allergens in food.
11. Methods for the detection of allergens and allergenic ingredients in food	Food & Drink Federation	Specific Comments • (Line 2002) –ELISA's cannot be regarded as fully 'qualitative' given issues with calibrants / antibodies etc. • Line 2008) – The section would benefit from a reference to any validation required by user prior to use for kit or any matrix validation and by considering the uncertainty of measurement for biological assays which can be significant.The expression of results 0.07mg/kg for an ELISA (2011) is unrealistic when analysing real samples. • (Line 2017) – No mention of analytical approaches to elucidate false positives i.e. robust matrix validation (re. analytical annex in FoodDrinkEurope guidelines on allergen management) • (Lines 2024- 2026) CRMs – Reference materials are commercially available from different producers for most major allergens but results may not be comparable. Further explanation is needed to justify why CRMs are not comparable.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• (Line 2023) – Overlook work undertaken at a member-state level to approve test methodology ISO / DIN standards • (Lines 2028-2030) – many of the CRM's cited are not clinically relevant or have not been certified specifically for allergen testing – issues with milk CRM irradiated and proven to be highly lactosylated • (Line 2037) - LFDs can be semi-quantitative; there is no discussion of the limitations associated with these assays as is highlighted for the ELISA section (e.g. matrix interference inter and intra assay variations, batch to batch variation). Additionally no mention that they require any validation. • (Line 2081) the influence of the different calibrators used should be reported. • (Line 2127) LCMS/MS is cited as being fit for purpose for quantification of allergen whereas its currently just quantification of peptide fragments and difficult to correlate back to the amount of allergenic protein – most of the work undertaken with MS is based on spiked not incurred materials • (Line2178) Overlooks the issues of effectiveness of trypic digest in accurate analysis of samples • (Lines2186-2188) quantif ication is not possible because of lack of reference materials, but not for ELISA – when results can be expressed as mg food/kg • (Line 2197) – the key interferences associated with this method of analysis – inhibition metals / fats etc. should be taken into consideration. • (Line 2239) Mention of mitochondrial DNA – must be pointed out that this makes the quantification impossible as amount/number of mitochondria will vary depending on cellular function. Competition is a key consideration for multiplexing PCR and must be taken into consideration • (Lines 2302-2305) Expression of results as of copy number of DNA it is not helpful to end user. This can be quantified, but better as mg food w/w –can be done through validation and is cited further in the Opinion • (Line 2319) –the use of reductive agents in sample extraction (mercaptoethanol) for highly processed foods should be taken into consideration • (Line 2344) – Overlooks that reliable incurred samples would still first require internationa lly agreed approved reference materials
11. Methods for the detection of allergens and allergenic	R-Biopharm AG	1971 Mention „fitness for purpose“ of a method and explain differences to classical validation approaches 1984 add “or PCT process” 1986 not allergenic is also possible. Its not relevant to detect only allergenic proteins of a commodity

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
ingredients in food		2002 change standards to calibrators 2016 there are at the moment no real RMs! Therefore the results differ due to different calibrator substances/preparations! 2018 monoclonal antibodies should be prefertially used for the development of ELISA methods, to minimize cross-reactivity and keep the quality of methods for a long term period 2023 please actualize R-Biopharm and Romer test kits within the last years! 2025 please discuss if certified reference materials are possible for allergens and not just cite "CRMs". Refer to Lacorn/Immer/Weiss publications 2030 so please do not name them under the chapter CRMs, MoniQA and an expert panel will try to develop materials in the future, Poster published by Roland Poms at the 8th workshop on food allergens methodologies (Towar ds the production of reference materials for food allergen and gluten-free analysis for improved food safety management) 2132 bottom up and top-down are occupied by uncertainty calculation and are misleading in the area of allergens 2136/2137 What is shotgun proteomics? 2154 Citation is missing 2162 What is the background or explanation or need to detect protein modifications? 2164 Delete this sentence because there is no explanation or further discussion 2163-2184 Discuss the publications critically: It is impossible until now to recalculate the result of a peptide quantification to the protein concentration since reference materials ("anchor points") are missing 2186-2191 Give examples for allergens 2202 One example for a reference materials for DNA analysis, otherwise rewrite this chapter. Discuss the fact that no one ever related the protein content to the DNA amount in the sample. What is traceability in this case? OWN CHAPTER FOR RMs and CRMs Describe also cases where LoD for a DNA-based metho ds e.g. in chocolate was very high (about 10-50 mg/kg) 2241 Also commercially 4plex PCR quantitative available 2316 e.g. gelatin does not contain DNA, but a high amount of protein 2326 Describe the range of recoveries for DNA extraction kits 2331 please add "most" before antibodies raised against the native form, because some commercially available ELISA methods detect denatured proteins (R-Biopharm soya detection kit, Morinaga egg detection kit) 2336 Also cite assays that are able to quantify ß-lactoglobulin and casein even in complex matrices (e.g. Johnson et al. 2013; Food Chemistry, 148:30-36, 2014) 2344 This sentence seems not to fit at this position in the text body 2346 ELISA are the best validated methods. Several parameters have been evaluated in independent collaborative studies (AOAC-RI for peanut and gliadin; AOAC-OMA for gliadin, CEN for hazelnut). An advantage of ELISA is that they can be easily validated by end-user in using spiking experiments. 2353 variation between batches is specula tive! Please give citation to proof this statement 2349-2356 The whole chapter is influenced by a preliminary and personnel opinion (and choice of literature) of the author(s) which is frankly far away from reality. Please change accordingly. 2357-2362 Please include the fact that there are only a few methods that are able to quantify. Most of the papers describe

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		qualitative method or the calibrator is not traceable to a protein 2364 However, there are also effects of disturbing substances on the detection of DNA, e.g. hemoglobin or spices. 2365 The DNA extraction of unknown samples is not established or validated
11. Methods for the detection of allergens and allergenic ingredients in food	The iFAAM FP7 Project	Given the remit from FSAI regarding DNA-based methods of detection, there is an important omission in this section. Specifically, it does not clearly state that DNA methods do not measure the amount of protein present. It does not elaborate on the possibility of false negatives (not enough DNA), false positives (similar species, improper primers) and how the results can be used in risk assessment. Section 11 also does not discuss the context in which analytical methods should be applied. Analytical results are only useful if the samples analysed have been taken as part of a correctly designed study, with a clearly defined aim, so that the sampling procedures and subsequent analyses are correctly designed/selected and implemented. Similarly, it does not discuss how different techniques can be used in a complementary manner nor does the section comment on the application of analytical methods under various circumstances, or to developing or validating risk assessments. Also, in this section, as well as in othe rs, examples of limit of detection (LoD) and limit of quantification values are stated (e.g. 1 and 4 mg/L) without reference to what the units are (e.g. mg/L protein/peptide/foodstuff). Without this information the LoD values referenced are essentially meaningless. This section (specifically lines 2135-2163) compounds the errors in section 8 (lines 1665-1676). The list of MS/MS capable instruments does not include, e.g. orbital ion traps. A distinction between methods capable of detecting the chemical entity which causes the risk (i.e. protein allergens) and those which use the presence of a (generally coincident) molecule (i.e. DNA) is crucial, and is needed to address the original request from the FSAI. Different processing may affect the relative recovery of DNA and protein allergens which could potentially lead to false negative or positive results. There is no distinction between methods used for research and those used for analysis for regulatory enforcement. This would be extremely helpful to those u nfamiliar with the methodology. It should be noted that C12 light isotope tagged peptides are not generally used for quantitation of allergens but rather 13C/15N peptides are used. Quantitative MS methods detect molar amount of peptide which must then be converted to a mass of protein and/or foodstuff. Relating to the need for (certified) reference materials the Opinion is consistent with the food allergy guidelines (Muraro et al Allergy. 2014 doi: 10.1111/all.12453.) where similar observations were made. It is critical that in any discussion of reference and certified reference materials that these terms be properly defined. We suggest ISO guide 30 as a reference for definitions of the terms CRM and RM. Section 11.2.4, line 2305 suggests certified reference materials available for allergenic food stuffs - as these have been used for DNA equivalence studies – but this is at odds with the highlighted lack of certified reference materials repeatedly mentioned elsewhere in section 11. We are unaware of the ex istence of a peanut CRM which fulfils the criteria of ISO guide 30 (e.g. metrological traceability). CRMs are important but a great deal can still be achieved whilst they are developed. Some particularly pertinent references are not cited e.g. Johnson PE et al (Food Chemistry 148 (2014) 30–36; available online 29 September 2013, which reports a ring trial using 2 different allergenic foods and several different kits using a quality control material with many attributes that could lead to this being developed as a CRM. To that end this has been developed as a quality control material which is now available to purchase (https://www.lgcstandards.com/epages/LGC.sf/en_GB/?ObjectPath=/Shops/LGC/Products/LGCQC101-KT).
11. Methods for the	VITAL Scientific	lines 1949-219

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
detection of allergens and allergenic ingredients in food	Expert Panel (VSEP)	Section 11 does not discuss the context in which analytical methods should be applied. Analytical results are only useful if the samples analysed have been taken as part of a correctly designed study, with a clearly defined aim, so that the sampling procedures and subsequent analyses are correctly designed/selected and implemented. Along the same lines, it does not discuss how different techniques can be used in a complementary manner. The section does not comment on the application of different analytical methods under various circumstances, nor how they can be used in developing or validating risk assessments or to support and validate HACCP based food safety systems intended to minimise or prevent allergen cross-contact.
12. Determination of thresholds for allergenic foods/ingredients	Deutscher Allergie- und Asthmabund	lines 2375 - 2530 - Public authorities and Food manufacturers need to apply risk assessment regarding unintended allergen presence in food products. The problem for both is the lack of agreed threshold doses that would support development of reference doses. For some of the important food allergens such as peanut, hazelnut, milk and egg a substantial number published data are available. Though data gaps exist for some foods, it should be considered that the available data result from studies with humans and do not require extrapolation as data obtained from animal studies do. - The prolific and inconsistent use of voluntary precautionary allergen labelling (PAL) on pre-packaged foods presents allergic consumers with significant challenges. Some allergic consumers ignore all such warnings, believing that they are used purely to protect food manufacturers from litigation. Thus they may be ignoring warnings on products that carry a very real and significant risk of contamination from major allergens and ma y put themselves at considerable risk. Alternatively, there are those that will avoid any product that carries any such warning, resulting in severely restricted food choice. The establishment of agreed threshold levels for the major allergens would provide the food industry with a sound basis for assessing the risk from the unintended presence of allergens in food, for trying to reduce cross-contamination to below the threshold levels and for making the use of PAL transparent and meaningful to allergic consumers .This should result in providing food-allergic consumers with more informed food choices and a greater level of protection. - As the new Food Information Regulation (1169/2011) allowed for the adoption of implementing acts relating to the possible and unintentional presence in food of substances for products causing allergies or intolerances , the significance and importance of establishing agreed threshold levels is highlighted . - A key reference with data regarding thresholds, which inclu des data from the EU funded EuroPrevall Project is the FSA report “Management of food allergens: from threshold doses to analysis in foods” (http://www.foodbase.org.uk//admintools/reportdocuments/830-1-1515_FS231067_Final_report_for_web_Sept_2013.pdf) has not been included in the Opinion - Learning from others: Japan already has established regulated reference doses for the unintended presence of food

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		allergens in food products with 10mg/kg protein of the allergenic food for milk, egg peanut, wheat and buckwheat. With milk, egg and peanut experience and comprehensive data for clinical thresholds and a risk based approach for reference doses exists for important allergens. According to personal message from Prof. Motohiro Ebisawa (internationally known and acknowledged allergy expert from Japan) allergic reactions rarely occur in Japan since the implementation of this regulation. Professor Ebisawa, states that the main causes of these reactions are allergenic ingredients that have not been labelled . If the unintended presence of food allergens below the threshold of 10 ppm causes a reaction, these reactions are mild. He also sees one of the major advantages of the establishment of thresholds to be the improvement in quality of life for allergic consumers. The experiences from Japan should be taken into consideration, when conclusions are drawn about the establishment of thresholds in Europe. Akiyma H, Imai T, Ebisawa M, 2011, Japan Food Allergen Labeling Regulation—History and Evaluation. In Steve L. Taylor, editor: Advances in Food and Nutrition Research, Vol. 62,Burlington: Academic Press, 2011, pp.139-171.
12. Determination of thresholds for allergenic foods/ingredients	Deutscher Allergie- und Asthmabund	Lines 2406 – 2407 A reason why the Panel states that safe thresholds cannot be established is, because patients with a history of severe allergic reactions are not challenged. This may be true in general for clinical practice regarding oral food challenges, when clinical history and tests (SPT or IgE) are matching and exposing those patients with the risk of a severe allergic reaction would pose an unnecessary burden upon the allergic patient. Nevertheless data from patients with severe reactions and / or at risk of anaphylaxis exist from the French Anaphylaxis Registry (Taylor SL et al 2010. Threshold dose for peanut: Risk characterization based upon diagnostic oral challenge of a series of 286 peanut-allergic individuals. Food Chem Toxicol, 48, 814-819.) as well as from oral immunotherapy studies, in which exactly patients with severe reactions are included. It should also be considered that patients experiencing the most severe allergic reactions are not necessarily those who react to minute amounts. It has been shown, that severe reactions are more likely to occur, when a larger amount of allergen has been consumed. Lines 2510 - 2514 It is correct that individual thresholds are variable and most patients do not know them. Ongoing research such as the FSA / UK TRACE study and the EU iFAAM project are also seeking to demonstrate in which way reactions and individual threshold levels can vary under certain circumstances in the same individual. Currently there is no practical consequence for an allergic consumer to know their own threshold, because he/ she cannot use it for his / her own risk assessment with no food available that is labeled accordingly. The determination of thresholds/ reference doses would assist clinicians in undertaking more effective testing in their patients and enable them to offer clearer and more helpful dietary advice.
12. Determination of	Deutscher Allergie-	Lines 2516 - 2517

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
thresholds for allergenic foods/ingredients	und Asthmabund	"Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer" EFSA's statement regarding "safe thresholds" does not take into consideration conclusions drawn from discussions at various international stakeholder meetings on this topic (e.g. Europrevall/ FSA meeting in Vienna 2012, ILSI meeting in Reading 2013). Discussions at these meetings concluded that 100% safety for all allergic consumers from any kind of allergic reaction is neither achievable nor realistic. A certain level of risk of allergic reaction will always be present for the most sensitive allergic consumers, BUT the establishment of thresholds/ reference doses as a basis for labelling should protect allergic consumers from severe reactions. The protection of every allergic consumer from every allergic reaction is not feasible nor is it supported by patient stakeholder groups. Undertaking to determine ze ro risk for all allergic consumers would mean that threshold levels are unlikely ever to be agreed. Finally, but importantly, in addition to helping to minimise risk, the establishment of standards for Risk Assessment defined by agreed threshold levels would improve the Quality of Life (QoL) of food allergic consumers by: • increasing informed consumer choice when shopping for food • generating greater trust in food labels • Improving the transparency and consistency of food labelling • minimising anxiety when food shopping • allowing greater consistency in allergen management throughout the food industry • enabling better communication to healthcare providers and consumers on the meaning of PAL Conclusion/ Ideas - 100% protection of every allergic consumer from every allergic reaction, i.e. zero risk, is not possible. If that is the aim/ goal allergen labelling based on thresholds / reference doses would not be possible. - Even if there are no sufficient data for the establish ment of thresholds/ reference doses available for all allergens, sufficient data do exist for very important allergens such as peanut, hazelnut, milk and egg. These could form the basis for a standardized (mandatory) risk assessment approach. Initially, thresholds/reference doses could be established for those allergens for which sufficient data exist, allowing time for more data for other allergens to be collated and reference doses established at a later date. - Standards that have been agreed and accepted will enable allergy clinicians, including dietitians to use a unified approach in advising and counselling their food allergic patients regarding the unintended presence of allergens. - By establishing standards for the Risk Assessment of unintended allergen presence, allergic consumers will be empowered to make informed choices for their own safety. Greater transparency in food labelling will lead to less uncertainty resulting in improved Quality of Life.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		We want to ask EFSA to consider the re-evaluation of the topic of thresholds/ reference doses taking into consideration additional references mentioned and focusing initially on those allergens that have already been studied and for which a large number of data exist, such as milk, egg, peanut and hazelnut. Taking into account that ongoing research will provide additional data in due course, these data could be included when available without starting a completely new evaluation by EFSA
12. Determination of thresholds for allergenic foods/ingredients	EAACI	Food producers and public authorities need to undertake risk assessment of presence of unintended allergenic food. The problem for both groups is the lack of agreed threshold doses that would support development of reference doses. A large body of published data are available for peanut, and whilst the evidence base for other allergenic foods is less substantial, efforts are underway to enhance it and data will be available in the coming few years. It is worth noting that whilst data gaps may exist, food allergy risk assessment has, as a food hazard, the benefit that it is based on data from humans and does not require, as if often the case, extrapolation of data obtained from animal models. The term "threshold" is incorrectly used in the opinion interchangeably with eliciting dose (ED) which leads to a lack of clarity. The opinion states "occurrence and intake data, studies used to derive individual thresholds". Neither occurrence nor intake data are used to calculate population thresholds (see line 2395-2 400). The opinion does not distinguishing, between the bench mark does (BMD) approach and probabilistic risk assessment. Specifically the description of ED 01 etc. starting at line 2461 should rightly start below the BMD approach line 2451. Calculating an ED 01, 05 or 10 is equivalent to a BMD and using it together with an estimated intake (e.g. the mean intake or the 95% percentile of the intake) opens the possibility to calculate a MoE and hence to decide if a contamination is acceptable or not. This method does not give an estimated risk in line with most other toxicological risk assessments. The probabilistic risk assessment does not use the ED01-10 but the whole distribution of challenge results as well as the distribution of intake. The outcome of a probabilistic risk assessment is an estimated risk. It is stated that published ED01-10 doses vary, yet inspection of Appendix A shows that only one publication that gives rather different ED results is Eller et al. 2012. Eller explains that the data are historical and comes from consecutive patients and that the starting dose is relatively high which explains the high ED's. As an example 5 of 7 first dose peanut reactors underwent double blind challenge (DBPCFC) with a starting dose of 85 mg peanut. This is not described or commented on in the opinion. The opinion describe that ED's vary among publication "depending" on "the decisions made by expert committees regarding the amount and characteristics of the challenge studies used, the distribution models applied, and the approach followed". This implies that the expert committees are including data, not depending on the quality of the data, but for other reasons and that if they had chosen otherwise, the result would have been very different. No evidence to support this conclusion is presented in the opinion. A criticism of the currently available data is that patients with a history of experiencing severe reactions are not challenged. This may be true in many studies, but a notable exception is the Eller et al publication where the highest ED10's included patients with a history of severe reactions. Eller et al concluded that the severity of a reaction was not associated with a low threshold dose. The review of available data misses key references, such

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		as the FSA report "Management of food allergens: from threshold doses to analysis in foods" (http://www.foodbase.org.uk//admintools/reportdocuments/830-1-1515_FS231067_Final_report_for_web_Sept_2013.pdf) which includes data from the extensive EuroPrevall study. The opinion does not define "safe" or "adverse reaction". Without clearly stating it, the conclusion implies, that no risk is accepted "safe allergen threshold levels that would not trigger adverse reactions".
12. Determination of thresholds for allergenic foods/ingredients	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	Abolishing precautionary labelling is one of the EFA's long-term priorities, as patients believe that "may contain" labels reduce the choices available to consumers, as it is impossible to know if a particular food with a precautionary label contains the allergen and how much of it is potentially inside. It is in many packaging and, as in some cases products with these labels do not contain residues of allergens or very small quantities that are unlikely to cause a clinical reaction; it may therefore lead to unnecessary restrictive diets. - In a study from 10 European countries of over 500 types of biscuits and chocolate, "may contain" labelling for nuts is included on the packaging of 26% of biscuits and 80% of chocolate – regardless of the label [1] It is likely that 90% of products with "precautionary labelling" do not contain residues of peanuts' proteins or very small quantities unlikely to cause a clinical reaction – starts an unnecessary restrictive diet [2] As a consequence, often people with all ergy feel frustrated and they have risk-taking behaviours due to: - Variety of the wording: 80% of parents with children who are allergic to nuts would not let them eat products with "not suitable for" or "may contain" labelling, only 50% would do so with "cannot guarantee nut free," "may contain traces of" labelling - Distrustfulness of the message sources: food business operators are deemed to use it to discharge any possible liability in case of adverse reactions following the ingestion of their products - Implausibility of the labelling: either when it is located on products that legitimately contain the allergen (e.g.: nuts in a packet of peanuts) or on others where it is considered impossible that they actually contain it (e.g.: nuts in a bottle of lemonade) - Previous experience and personal preferences [3] However, serious reactions, and even deaths, have been caused by foods with "may contain" labelling (8% of people with accidental reactions may attribute it to having ignored a "precautiona ry labelling"). If there is enough data for some of the allergen, EFSA could start by identifying possible thresholds and leave the others unregulated. Risk assessment methods would require the involvement of healthcare professionals and patients as they are the ones taking the risks and they should be involved in the decisions influencing their health. Legislation regulating precautionary labelling already exists in some countries. After thresholds set in Japan in 2001, reported allergic reactions were mostly caused by illegal labelling and they were mainly associated with mild symptoms. Unfortunately, in Switzerland, there are not enough studies and patients' data on this topic to evaluate the legislation on the labelling and advertising of food products to show a decrease in anaphylaxis cases after the entry into force of the law regulating precautionary labelling. In a short-term, precautionary labelling could possibly be used only as an ultimate solution after the implementation of best-

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		practices to a void cross-contamination (e.g.: allergen management as part of hygiene/safety manual, responsibility of food business operators at each step of the distribution chain). The establishment of thresholds should not undermine patients' safety. If EFSA cannot find the right scientific evidence for establishing thresholds, then it is the responsibility of food business operators to guarantee that cross-contamination is avoided and thus "may contain" is not used. The new food information to consumers regulation still requires the Commission to adopt an implementing act (there is no deadline for this) on different ways Member States adopt precautionary labels. The opinion could have helped the Commission doing this.
12. Determination of thresholds for allergenic foods/ingredients	European Federation of Allergy and Airways Diseases Patients' Associations (EFA)	Analytical methods thresholds must be added too. We must obtain some clear "typology" of thresholds regarding not only "how much" but also "how" and "why". Individual sensibilities are used to determinate population ones. EFSA concludes (line 2516) that there is not enough scientific evidences to give them and it doesn't provide any definition of "severe", "mild" reaction neither. Those might be used by political bodies to fix "official" threshold once they'll decide the % of person that can reasonably be protected by consuming "standard" foods (regarding a reasonable daily intake of various foods). We must also imagine thresholds to protect consumers of "free from" products (that might be more expensive of course for consumers). Now we must "translate" those thresholds on food content. Those thresholds will be used on the quality management system of food producers all through the food chain. First to test a new line, a new recipe before production and second during production to verify. Thresholds must , of course, also be used in laboratory: the food producer lab or its analytical supplier must realise analyses (quantitative or qualitative) and conclude if yes or no there is this ingredient on the product and how much. However, analytical methods usually dose only a part of the ingredient (for example only cor8 protein for hazelnut). After all that decision must be taken: take a decision of labelling or there is no obligatory link between internal quality management and label. That is indeed the case for chemical (pesticides content) or bacteriological (salmonella or listeria monocytogenes) or even physical (for example piece of glasses) contaminants. In the mind of several stakeholders, it seems to be taken for granted that thresholds are dedicated to label decision. In HACCP method, they must be used as quality management decision (that means whether the product is conformed or not, if not it should not be sold) that are not systematically translated in label (would we accept "may contain bacteria" as a warning sticker?). It is thus possible to define thresholds which must be used in HACCP and not appear on label. It is exactly the case in animal feed for example.
12. Determination of thresholds for allergenic foods/ingredients	FEDIOL	As mentioned in the draft opinion, FEDIOL agrees with the importance of qualitative and quantitative data in order to set relevant thresholds particularly, given that an allergen can sometimes trigger a severe response, which could relate to exposure to a very small amount. FEDIOL is aware that a considerable volume of data has been obtained under controlled food challenge conditions and that approaches have been published which demonstrate how these data can be used effectively in quantitative risk assessment. FEDIOL believes that transparent analysis of these data and results require EFSA to set clear criteria and guidance, including on the adverse outcome of importance, and on quality criteria for inclusion and exclusion of studies from consideration.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Furthermore, FEDIOL considers that other expertise available within EFSA could usefully be deployed to answer these admittedly difficult questions. This would enable EFSA to further assess those studies mentioned in section 12 and rate them accordingl y. Such additional analysis could further help to determine safe allergen threshold levels based on sound dose distributions and revise ultimately the current conclusions under section 12.5.
12. Determination of thresholds for allergenic foods/ingredients	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
12. Determination of thresholds for allergenic foods/ingredients	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
12. Determination of thresholds for allergenic foods/ingredients	FoodDrinkEurope	12 – Determination of thresholds for allergenic foods/ingredients – general comments on section (lines 2375-2530) This section covers the basis for risk assessment of allergenic foods and is therefore critical to this report and fulfilling the terms of reference. The report describes approaches for determining thresholds for allergenic foods or ingredients. It starts by defining several terms and then proceeds to describe the determination of individual thresholds (based on DBPCFC) and population thresholds. Given that risk assessment is at the heart of the mandate the expectation was that this section would contain rigorous, critical analyses of the different approaches available and their limitations, leading to a conclusion on

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		suitability and domains of applicability. A number of issues arise with this section: - Definition of terms. It would have been useful to elaborate on the meaning of threshold and its use in different and very distinct contexts – Kroes et al (2000) provide a good context, which has been cited elsewhere. Researchers, clinicians and others working in this area have moved away from using the term threshold, except for individual responses, because of the high probability of generating confusion over different concepts (e.g. population thresholds, regulatory thresholds, management thresholds). This has been extensively discussed in Crevel et al (2007) and other publications. This section could also have provided an opportunity to define "adverse reactions". These should bear a relevance to general understanding and reference other uses. For instance, the pharmaceutical industry has standardized the criteria for adverse events. Signs and symptoms are categorised as mild, moderate, or severe, often depending upon whether the symptoms interfere with the subject's daily activities. Relatively mild symptoms are transient with no significant disruption of daily life. Using this methodology, mild symptoms and would not be classed as "adverse effects", while moderate and severe symptoms could be considered as a risk to human health. - Kroes R, Galli C, Munro I, Schilter B, Würtzen G. Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. Food Chem Toxicol 2000:38, 255-312. - Crevel RWR, Briggs D, Hefle SL, Knulst AC, Taylor SL. Hazard characterization in food allergen risk assessment: the application of statistical approaches and the use of clinical data. Food Chem Toxicol 2007; 45(5):691-701 - Data analysis. The strategy and approach to the analysis of data on minimum eliciting doses (MEDs) are not easy to discern. In particular it is unclear how they have taken into account the quality of data from different sources. - Data quality. The Opinion comments on the variability of the ED values emanating from different studies. This issue is related to the above one of data quality and we would therefore suggest that the studies in question are considered critically, rated in terms of quality and transparent conclusions drawn. This may well lead to the elimination of certain outlying values and thereby help to resolve the issue. The Opinion mentions that decisions on selection of data are not transparent. However, at least for the peer-reviewed publications emanating from the VSEP (Allen et al 2014, Taylor et al 2014), the criteria are set out quite explicitly. These are also reiterated in Crevel et al (2014). In addition, the selection and use of data sources is not completely clear: a thesis by Ben Remington (University of Nebraska – Lincoln) is cited, but a report on the Europrevall threshold data, available publically from the UK FSA website does not seem to have been accessed.
12. Determination of thresholds for allergenic foods/ingredients	FoodDrinkEurope	- 12.2 Determination of thresholds for an individual – comments (lines 2401-2429) The limitations of DBPCFC are mentioned, in particular the exclusion of people with a prior history of severe reactions and the variety of protocols which have been employed. o exclusion of people with a prior history is commonly cited in many publications, but the magnitude of the issue (how many people excluded out of how many tested) is not mentioned despite the fact that it is critical to quantitative risk assessment. Exclusion of people with severe reactions is almost always equated to exclusion of most sensitive individuals, even though the two terms are not synonymous and it is based on an unproven assumption. Individuals participating in DBPCFC studies that have been reported to date are rarely, if ever, a random selection of the at risk (allergic) population. Indeed the vast

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		majority of low dose DBPCFC studies have included patients referred to specialist allergy clinics in tertiary care centres, such that the cha llenged population could be considered skewed towards the more reactive/affected members of the food allergic population. The dose which provoked a severe reaction in a community (free-living) situation is usually inadequately documented. Indeed the epidemiology of severe reactions tends to indicate that severe reactions are associated with relatively large exposures to the offending allergenic food (Pumphrey et al). With regards to the variety of protocols, it should also be taken into consideration that since their last Opinion was published, considerable efforts have been made to harmonise protocols (Taylor et al 2004, Crevel et al 2008 and others), including many of the variables listed in Table 4 (e.g. administration protocols, form of food, etc). A considerable volume of data has been generated using these harmonised protocols or versions similar to them, thereby improving the quality of data available for dose distribution modelling., while it is mentioned that most DBPCFCs have been conducted for diagnostic purposes rather than to establish individual thresholds it is not mentioned that many of those results have been excluded from dose-distribution modelling (see 12.3) in order to avoid bias due to left-censoring of a significant number of observations to a relatively high value. Furthermore, a similar list of shortcomings could be drawn up for classical toxicological studies, which are well-accepted as a basis for risk assessment (and used regularly by other EFSA Panels), demonstrating that the available DBPCFC data can indeed be used for risk assessment. While it is considered that the available data are insufficient to reach a conclusion on thresholds for any of the allergenic foods on Annex II, guidance on what is considered sufficient would be appreciated.
12. Determination of thresholds for allergenic foods/ingredients	FoodDrinkEurope	12.3 Determination of thresholds in a population – comments (lines 2430-2503) - Risk assessment approaches. The report reviews three different risk assessment approaches, as described in Madsen et al (2009): the safety assessment approach, the benchmark dose (BMD) approach and probabilistic models. Conclusions regarding the suitability of particular approaches are not drawn, which means that it also provides no guidance as to future directions for research and data generation. o On the safety/traditional risk assessment approach, the conclusion (lines 2442-2445) is difficult to understand. The doses to which people may react are indeed very variable, although recent studies have documented the actual range (around 6 orders of magnitude). Since the lower end of the dose distribution is now well-documented, determining a benchmark (threshold) is a textbook exercise in applying selected uncertainty factors to the NOAEL or LOAEL, depending on which is available. In determining an appropriate point of departur e, the main consideration would be data quality. Madsen et al (2009) identified the main weakness in this approach, and why it is therefore not appropriate as "regulatory thresholds which are below those that can be reasonably attained in general food manufacturing, and indeed below those that could be reliably measured with current assays." o The report outlines very briefly the BMD approach, but omits any mention of the excellent EFSA Opinion on this topic, which concluded that "the BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a Reference Point, since it makes extended use of available dose-response data and it provides a quantification of the

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		uncertainties in the dose-response data."(EFSA 2009). o The report also outlines very briefly the probabilistic risk assessment approach, although it seems to conflate this with eliciting doses, whereas its main output is actually an estimate of the likely number of reactions, given a particular pattern of exposure, not an ED value. Furthermore, it omits to discuss several recent pertinent studies, such as those of Rimbaud et al (2010) on peanut, Probabilistic risk assessment models as currently implemented without exception over-predict the number of reactions, compared to the number that can be reasonably estimated from publically available data. The issue has been recognised and discussed (e.g. Crevel et al 2014) and is thought to arise as a consequence of the type of population enrolled in challenge studies as well as the fact that the models are currently unable to discriminate between different degrees of reaction in terms of severity. Only a proportion, currently unknown, of the reactions would reach health care practitioners and be captured in any reporting system. o Dose distribution models themselves are not based on expert judgement: this is only used to guide the decision on the combined ED value derived from the different distribution models, which weights more heavily those which provide a good fit at the lower end of the curve. o It is stated (Line 2494) that there is no standard methodology to calculate population thresholds. This is correct in a very limited way, since the approaches described both in this Opinion and elsewhere (e.g. Madsen et al 2009) are designed to characterise the hazard, not to define a population threshold, a concept which inherently requires a judgement to be made about the acceptability of the risk. However taking a broader view, dose distribution modelling in fact uses a fairly standard methodology i.e. a BMD approach to define a point of departure
12. Determination of thresholds for allergenic foods/ingredients	FoodDrinkEurope	12.3 Determination of thresholds in a population – comments (lines 2430-2503) Madsen, C.B., Hattersley, S., Buck, J., Gendel, S.M., Houben, G.F., Hourihane, J.O.,Mackie, A., Mills, E.N., Norhede, P., Taylor, S.L., Crevel, R.W., 2009. Approaches to risk assessment in food allergy: report from a workshop ''developing a framework for assessing the risk from allergenic foods''. Food Chem. Toxicol. 47, 480–489. Rimbaud, L., Heraud, F., La Vieille, S., Leblanc, J.C., Crepet, A., 2010. Quantitative risk assessment relating to adventitious presence of allergens in food: a probabilistic model applied to peanut in chocolate. Risk Anal. 30, 7–19.
12. Determination of thresholds for allergenic foods/ingredients	FoodDrinkEurope	12.4 Prediction of individual sensitivity – comments (lines 2504-2514) - We agree with the contents of subsection 12.4 and would point out that it has never been suggested that population thresholds should be used directly for management of food allergy at the individual level. Indeed it highlights the importance of addressing the whole issue of the safety of allergic individuals as a shared responsibility between the different stakeholders, including people with food allergies.
12. Determination of thresholds for allergenic foods/ingredients	FoodDrinkEurope	12.5 Conclusion – comments (lines 2515-2530) It is concluded that "Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer". As it is described in Section 3, clinical symptoms of food allergy range from subjective signs (not evident to an external observer) to mild objective symptoms through to multi-organ symptoms, as in anaphylaxis. These are clearly not equivalent in terms of their impact on health or quality of life. Since it is not defined what an adverse reaction is, it is unlikely that any evidence can be produced that will

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		demonstrate a No Adverse Effect Level at a population level, based on such criteria. Indeed, the likelihood that such population thresholds could not be defined was one of the main drivers for the development of the dose distribution modelling approach as discussed in Crevel et al (2007). - As a consequence of not defining "adverse reactions" and thereby no t being able to define "safe allergen thresholds" in a meaningful way, the question posed by the FSAI on thresholds was not addressed. - Taken as a whole, the conclusion lacks transparency as it does not naturally flow from the data and analysis in the preceding part of the section. We would submit that the Panel might like to note the parallel with classical toxicological data which are the foundation for safety assessment, as outlined below Variability of endpoints across studies: these can be equally or more variable in animal studies compared to food challenge studies Study design: animal studies are conducted according to rigidly standardised and codified criteria to minimise variability (GLP); they almost all use young adult, healthy animals, fed a completely balanced diet suitable for the test species. In comparison, while DBPCFC are standardised in terms of protocol, participants are not, and indeed cannot be standardised. They are thus arguably more representative of the population of interest, even bearing in mind the exclusion of certain sensitive individuals. Interpretation: interpreting findings from an animal study in terms of public health significance to human beings requires consideration of factors such as pharmacokinetics and pharmacodynamics peculiar to the species and even whether the critical endpoint is relevant to man. In food challenge studies, the endpoint of interest is the one that is studied and there is obviously no need for interspecies extrapolation.
12. Determination of thresholds for allergenic foods/ingredients	Food & Drink Federation	general comments on section (lines 2375-2530) This section covers the basis for risk assessment of allergenic foods and is therefore critical to the opinion and fulfilling the terms of reference. The Opinion describes approaches for determining thresholds for allergenic foods or ingredients. It defines several terms and goes on to describe the determination of individual thresholds and population thresholds. Given that risk assessment is at the heart of the initial mandate, it was expected that this section would contain rigorous, critical analyses of the different approaches available and their limitations, leading to a conclusion on suitability and domains of applicability. There are several issues with this section: - Definition of terms. It would have been useful if the opinion had elaborated on the meaning of threshold and its use in different and distinct contexts – Kroes et al (2000) provide a good context, which has been cited elsewhere. Researchers, clinicians and others working in this area ha ve moved away from using the term threshold, except for individual responses, because of generating confusion over different concepts (e.g. population thresholds, regulatory thresholds, management thresholds). This has been extensively discussed in Crevel et al (2007) and other publications. A definition of "adverse reactions", bearing a relevance to general understanding and referencing other uses would have been helpful in this section. For instance, mild symptoms may not be classed as "adverse effects", while moderate and severe symptoms could be considered as a risk to human health. - Kroes R, Galli C, Munro I, Schilter B, Würtzen G. Threshold of toxicological concern for chemical substances present in

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		the diet: a practical tool for assessing the need for toxicity testing. Food Chem Toxicol 2000:38, 255-312. Crevel RWR, Briggs D, Hefle SL, Knulst AC, Taylor SL. Hazard characterization in food allergen risk assessment: the application of statistical approaches and the use of clinical data. Food Chem Toxicol 2007; 45(5):691-701 - Data analysis. The strategy and approach to the analysis of data on minimum eliciting doses (MEDs) are not easy to discern. In particular, it is unclear how the Panel has taken into account the quality of data from different sources. - Data quality. The Opinion comments on the variability of the ED values emanating from different studies. This issue is related to that of data quality and we would therefore suggest that the studies in question are considered critically, rated in terms of quality and transparent conclusions drawn. This could lead to the elimination of certain outlying values and thereby help to resolve the issue. The opinion mentions that decisions on selection of data are not transparent. However, at least for the peer-reviewed publications emanating from the VSEP (Allen et al 2014, Taylor et al 2014), the criteria are set out quite explicitly. These are also reiterated in Crevel et al (2014). The selection and use of data sources is also unclear given that a thesis by Ben Remington (University of Nebraska - Lincoln) is cited, but a report on the Europrevall threshold data, available publically from the UK FSA website, does not appear to have been considered.
12. Determination of thresholds for allergenic foods/ingredients	Food & Drink Federation	- 12.2 Determination of thresholds for an individual – comments (lines 2401-2429) The limitations of DBPCFC are mentioned, in particular the exclusion of people with a prior history of severe reactions and the variety of protocols that have been employed. exclusion of people with a prior history is commonly cited in many publications. However, although the magnitude of the issue is critical to quantitative risk assessment, it is not covered. Exclusion of people with severe reactions is almost always equated to exclusion of most sensitive individuals, even though the two terms are not synonymous and it is based on an unproven assumption. Individuals participating in DBPCFC studies that have been reported to date are rarely, if ever, a random selection of the at risk (allergic) population. Indeed the vast majority of low dose DBPCFC studies have included patients referred to specialist allergy clinics in tertiary care centres, such that the challenged population could be considered skewed towards the more r eactive/affected members of the food allergic population. The dose which provoked a severe reaction in a community situation is usually inadequately documented. Indeed the epidemiology of severe reactions tends to indicate that severe reactions are associated with relatively large exposures to the offending allergenic food (Pumphrey et al). With regards to the variety of protocols, since the Panel's last Opinion was published, considerable efforts have been made to harmonise protocols (Taylor et al 2004, Crevel et al 2008 and others), including many of the variables listed in Table 4 (e.g. administration protocols, form of food, etc). A considerable volume of data has therefore been generated, using these harmonised protocols or versions similar to them, thereby improving the quality of data available for dose distribution modelling. While the opinion covers the fact that most DBPCFCs have been conducted for diagnostic purposes rather than to establish individual thresholds, it is not mentioned that man y of those results have been excluded from dose-distribution modelling (see 12.3) in order to avoid bias, due to left-censoring of a significant number of observations to a relatively high value.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Furthermore, a similar list of shortcomings could be drawn up for classical toxicological studies, which are well-accepted as a basis for risk assessment and used regularly by other EFSA Panels. This surely demonstrates that the available DBPCFC data can indeed be used for risk assessment. While it is considered that the available data are insufficient to reach a conclusion on thresholds for any of the allergenic foods in Annex II, industry would appreciate guidance on what is considered sufficient.
12. Determination of thresholds for allergenic foods/ingredients	Interassociation des personnes allergiques et intolérantes	EFSA panel concludes: "current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer". For reasons pointed in our previous comment, thresholds are needed for quality management purposes (not necessary linked with may contain label) either as a voluntary decision of food manufacturer or as an official decision. As EFSA points that it can't establish thresholds based on epidemiology, can it suggest other means? For example, consumers and control bodies might take advantage of better knowledge on reality of cross contamination in food manufacturers facilities (like UE knows in animal feed production). They also might take advantage of enquiry on other countries (Switzerland, Japan, New Zealand and Australia).
12. Determination of thresholds for allergenic foods/ingredients	nutrition counselling	line 2375 ff: Why were the data from EuroPrevall not considered? They provide data for 7 allergens and are available by the following link: http://www.foodbase.org.uk//admintools/reportdocuments/830-11515_FS231067_Final_report_for_web_Sept_2013.pdf In lines 2515-16 you state that "Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer." If the understanding of "safe" is "no reaction in any at-risk patient" there will never be a regulation for unintended presence of allergens. Why not adopt a concept such as the VITAL 2.0 described by (5) for regulation of cross-contamination? As allergen avoidance is the mainstay of management and avoidance of inadvertent exposure is of top priority for allergic consumers, labeling should provide necessary information about allergen content, including unintended presence. But, precautionary labeling should be restricted to those foods where an accepta ble level of protection for at-risk consumers cannot be guaranteed. Otherwise allergic consumers will ignore the precautionary labeling (3, 4). In line 2523 you state that patients at risk of severe reactions are excluded from challenge studies. This is definitely not true for all oral immunotherapy OIT studies, because this therapy is explicitly for patients at risk of severe reactions. 3. Monks H, Gowland MH, MacKenzie H, Erlewyn-Lajeunesse M, King R, Lucas JS, et al. How do teenagers manage their food allergies? Clinical and experimental allergy : journal of the British Society for Allergy and Clinical Immunology. 2010;40(10):1533-40. 4. Ben-Shoshan M, Sheth S, Harrington D, Soller L, Fragapane J, Joseph L, et al. Effect of precautionary statements on the purchasing practices of Canadians directly and indirectly affected by food allergies. The Journal of allergy and clinical immunology. 2012;129(5):1401-4. 5. Allen KJ, Remington BC, Baumert JL, Crevel RW, Houben GF, Brooke-Taylor S, et al. Allergen reference doses for precautionary labeling (VITAL 2.0): clinical implications. The Journal of allergy and clinical immunology. 2014;133(1):156-

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		64.
12. Determination of thresholds for allergenic foods/ingredients	The iFAAM FP7 Project	Risk assessment for unintended allergenic constituents is necessary for both food manufacturers and public authorities. A gap for both groups is the lack of agreed threshold doses that would support development of reference doses. The data available for this varies according to food with more data available for peanut than for other allergenic foods. Efforts are underway to improve the data. Food allergy risk assessment is based on data from human studies and does not require, as is the case with toxicological assessments, extrapolation of data obtained from animal studies. The terms "threshold" and "eliciting dose (ED)" should be defined and there should be clarity as to which is meant in each case. The Opinion states "occurrence and intake data, studies used to derive individual thresholds", whilst neither occurrence nor intake data are used to calculate population thresholds (see line 2395-2400). There is no distinction between bench mark dose (BMD) approach and probabilistic risk assessment. The descrip tion of ED 01 etc. (line 2461) should start below the BMD approach (line 2451). Calculating an ED 01, 05 or 10 is equivalent to a BMD and using it together with an estimated intake (e.g. the mean intake or the 95% percentile of the intake) opens the possibility to calculate a MoE and hence to decide if a contamination is acceptable or not. This method does not give an estimated risk in line with most other toxicological risk assessments. The probabilistic risk assessment does not use the ED01-10 but the whole distribution of challenge results as well as the distribution of intake. The outcome of a probabilistic risk assessment is an estimated risk. It is stated that published ED01-10 doses vary, yet Appendix A (Eller et al. 2012) shows the data are historical and come from consecutive patients and that the starting dose is relatively high which explains the high EDs. As an example 5 of 7 first dose peanut reactors underwent double blind challenge (DBPCFC) with a starting dose of 85 mg peanut. This is not d escribed in the Opinion. The Opinion describes that EDs vary among publication "depending" on "the decisions made by expert committees regarding the amount and characteristics of the challenge studies used, the distribution models applied, and the approach followed". This implies that the expert committees are including data, not depending on the quality of the data, but for other reasons. No evidence to support this conclusion is presented. A criticism of the available data is that patients with a history of experiencing severe reactions are not challenged. Whilst broadly true, a notable exception is Eller et al where the highest ED10's included patients with a history of severe reactions suggesting that the severity of a reaction was not associated with a low threshold dose. Another exception is patients entered in the French Anaphylaxis registry (Taylor S et al (2010) Food Chem Toxicol 48, 814 – 819) and patients in immunotherapy studies. The review of available data misses key references, e.g. the FSA rep ort (http://www.foodbase.org.uk//admintools/reportdocuments/830-1-1515_FS231067_Final_report_for_web_Sept_2013.pdf) which includes data from the extensive EuroPrevall study. The Opinion concludes (line 2516) "Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer". The Opinion does not define "safe" or "adverse reaction". The conclusion implies, that no risk is accepted "safe allergen threshold levels that would not trigger adverse reactions" even though all stakeholders recognise that zero risk is not achievable in practice (Madsen et al 2012 Clinical & Experimental Allergy, 2012 (42) 30–37).
12. Determination of thresholds for	TNO - Nederlandse Organisatie voor	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
allergenic foods/ingredients	Toegepast Natuurwetenschappelijk Onderzoek	The approach described in lines 2377-2379 ignores the international and intercontinental developments involving multiple stakeholders (including risk assessors and allergic patient groups) who consider a zero tolerance approach to not be feasible. These groups include, but are not limited to the ILSI Europe Food Allergy Task Force and the Allergen Bureau of Australia & New Zealand and their VITAL® (Voluntary Incidental Trace Allergen Labelling) system. Additional groups and workshops are exploring whether it is possible to come to accepting a small residual risk and defining thresholds or reference doses for precautionary labeling purposes. These approaches and discussions are discussed in detail in eg Madsen et al. (Regul Toxicol Pharmacol 2010, 57: 256-265; Food Chem Toxicol 2009, 47:480-489). Further, the EU is funding iFAAM Integrated approaches t o food allergen and allergy management (2013-2017), as follow up of the EuroPrevall EU project. It aims to Develop evidence-based approaches and tools for management of allergens in food and is based on the methodologies as mentioned in the above publications. Lines 2488-2493 refer to the reference doses for each of the allergens proposed for precautionary labeling purposes. The VITAL® scientific expert panel (VSEP) used a defined set of publications with clear literature search terms and established criteria for inclusion and extended their dataset by collecting unpublished data from established food allergy clinics that currently are either published (Blom et al 2013; Dambacher et al 2013) or submitted for publication or in preparation. A number, but not all of the publications used by the VSEP are also included in the current scientific opinion. It should be noted that the reference doses for precautionary labeling derived by the VSEP are for objective allergic symptoms and in general below the LOAEL s presented for each allergenic food in the draft Scientific Opinion (as in chapters 13-26, or are in the same order of magnitude as reported in the evaluation), or the VSEP panel could not derive a reference dose based on their criteria (mollusk, celery, fish etc for the dataset was not suitable to model a threshold distribution). Further, it should also be noted that the approach to address precautionary labeling taken by the VSEP panel and agreed upon by international stakeholders including ILSI and patient groups, is accepting that these doses will not protect a small part of the most sensitive allergic individuals of having mild transitory objective effects (i.e ≤ 1% of the allergic population).
12. Determination of thresholds for allergenic foods/ingredients	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. The paragraphs in Chapter 12 explaining the terminology and determination of thresholds are in some parts not completely clear, lacking information or not referring to the correct reference. Examples are, but not limited to: 2406-2408 “In addition, most clinicians exclude from challenge studies those patients likely to have the most severe reactions (i.e. highly sensitised individuals and those with history of anaphylaxis) based on the individual‘s history (Taylor et al., 2002).” It must be noted that a highly sensitive MOED does not indicate severe symptoms during an allergic reaction. Lines 2406-2408 However, while patient selection bias does occur and often excludes patients with a history of severe reactions, Taylor et al 2010 obtained data from a non-selective clinic and showed that no difference in ED values occurred when comparing patien ts with and without a history of severe allergic reactions.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Lines 2414-2416 Please look at Allen et al 2014 to see that the form of peanut (flour vs crushed) and milk (liquid vs NFDM) do not affect the population threshold distributions. Lines 2420-2425 This sentence is misleading as newer studies and newer consensus recommendations have changed dosing protocols to establish low mg individuals thresholds. 2452-2454 Remington et al 2013 is the only correct reference for demonstration of a probabilistic risk assessment, others would be Spanjersberg et al 2007;2010 and Kruizinga et al 2008. The other references refer to threshold dose distributions and not RA, and van Bilsen is neither. Lines 2462-2468 refer to the threshold dose distribution in an allergic population and the BMD approach, and is not in connection to the outcome of the probabilistic risk assessment as in described in line 2452-2461. These paragraphs and independent methods should be separated and properly detailed as confusions an d mixings occur in the current draft report. Lines 2452-2468 The concept of probabilistic risk assessment for food allergy does not seem to be fully understood in detail by the reviewers and the topic is mixed with the benchmark dose approach for determining a population reference dose. Corrections and separations are needed for this entire section. Ch 12 (lines 2477-2480) The Scientific Opinion reports data that shows differences (egg white vs whole egg) but not similarities in threshold data (forms of peanut or milk) and fails to report the wide confidence intervals associated with calculations and conclusions based on data sets of such low numbers compared to the milk and peanut data. Lines 2481-2482 The Scientific Opinion references Remington 2013 in other places but chooses not to report the analysis by Remington 2013 on the effect of geographical differences in calculated ED values. Why the inconsistency? 2498-2503 The Panel also notes the high variability among various population threshold s estimated for a same allergenic food/ingredient, and that the accuracy of these thresholds has not been tested yet prospectively in real life conditions (i.e. percentage of the allergic population actually reacting to a given dose of the allergic ingredient when consumed in different food matrices and eating occasions relative to the percentage of the allergic population estimated to react from population threshold curves). The accuracy of these threshold is currently being tested for peanut, milk, egg, and hazelnut using the protocol reported by Zurzolo et al 2013. Peanut is independently funded while milk, egg, and hazelnut are part of the previously mentioned iFAAM EU project.
12. Determination of thresholds for allergenic foods/ingredients	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. In line 2388 – 2429 the review is ignoring the developments made in the scientific and clinical diagnosis of food allergy since 2002 through the European Academy of Allergology and Clinical Immunology (EAACI) and in part of the EU funded

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Europrevall project (2007-2012). See below the references. This has led to the use of standardized protocols for the diagnosis of food allergy since then and is reflected in publications since. 1: Winberg A, Nordström L, Strinnholm Å, Nylander A, Jonsäll A, Rönmark E, West CE. New validated recipes for double-blind placebo-controlled low-dose food challenges. Pediatr Allergy Immunol. 2013 May;24(3):282-7. doi: 10.1111/pai.12061. PubMed PMID: 23590418. 2: Cochrane SA, Salt LJ, Wantling E, Rogers A, Coutts J, Ballmer-Weber BK, Fritsche P, Fernández-Rivas M, Reig I, Knulst A, Le TM, Asero R, Beyer K, Golding M, Crevel R, Clare Mills EN, Mackie AR. Development of a standardized low-dose double-blind placebo-controlled challenge vehicle for the EuroPrevall project. Allergy. 2012 Jan;67(1):107-13. doi: 10.1111/j.1398-9995.2011.02715.x. Epub 2011 Sep 19. PubMed PMID: 22092081. 3: Bindslev-Jensen C, Ballmer-Weber BK, Bengtsson U, Blanco C, Ebner C, Hourihane J, Knulst AC, Moneret-Vautrin DA, Nekam K, Niggemann B, Osterballe M, Ortolani C, Ring J, Schnopp C, Werfel T; European Academy of Allergology and Clinical Immunology. Standardization of food challenges in patients with immediate reactions to foods--position paper from the European Academy of Allergology and Clinical Immunology. Allergy. 2004 Jul;59(7):690-7. Review. PubMed PMID: 15180754. 4: Taylor SL, Hefle SL, Bindslev-Jensen C, Atkins FM, Andre C, Bruijnzeel-Koomen C, Burks AW, Bush RK, Ebisawa M, Eigenmann PA, Host A, Hourihane JO, Isolauri E, Hill DJ, Knulst A, Lack G, Sampson HA, Moneret-Vautrin DA, Rance F, Vadas PA, Yunginger JW, Zeiger RS, Salminen JW , Madsen C, Abbott P. A consensus protocol for the determination of the threshold doses for allergenic foods: how much is too much? Clin Exp Allergy. 2004 May;34(5):689-95. Review. PubMed PMID: 15144458. 5: Vlieg-Boerstra BJ, Bijleveld CM, van der Heide S, Beusekamp BJ, Wolt-Plompen SA, Kukler J, Brinkman J, Duiverman EJ, Dubois AE. Development and validation of challenge materials for double-blind, placebo-controlled food challenges in children. J Allergy Clin Immunol. 2004 Feb;113(2):341-6. PubMed PMID: 14767452.
12. Determination of thresholds for allergenic foods/ingredients	The Danish Veterinary and Food Administration	The Danish Food and Veterinary Administration supports the comments uploaded by Charlotte Bernhard Madsen from the National Food Institute, Technical University of Denmark. The EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA) was asked to deliver a scientific opinion on the evaluation of allergenic foods and food ingredients for labelling purposes. As a national authority we have to do the risk assessment on a regular basis and are calling for an agreed threshold. We hope that EFSA will work towards a solution in regard to an EU agreed method of risk assessment.
12. Determination of thresholds for allergenic	National Food Institute, Technical University of	The authors are not distinguishing, in an easy understandable way, between the BMD approach and probabilistic risk assessment. They mention the three approaches to risk assessment, as described in Madsen et al. 2009, but the description of ED 01 etc.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
foods/ingredients	Denmark	starting at line 2461 should rightly start below the BMD approach line 2451. Calculating an ED 01, 05 or 10 is equivalent to a BMD and using it together with an estimated intake (e.g. the mean intake or the 95% percentile of the intake) opens the possibility to calculate a MoE and hence to decide if a contamination is acceptable or not. This method does not give an estimated risk in line with most other toxicological risk assessments. The probabilistic risk assessment does not use the ED01-10 but the whole distribution of challenge results as well as the distribution of intake. The outcome of a probabilistic risk assessment is an estimated risk (more on the different risk assessments with examples can be found in Madsen et al 2014). In line 2494 the authors n ote that "there is no standard method to calculate population thresholds across allergenic foods". It is not clear what they mean by a standard method. They mention "occurrence and intake data, studies used to derive individual thresholds". Neither occurrence nor intake data are used to calculate population thresholds as the word is used in the opinion interchangeable with eliciting dose (ED) (see line 2395-2400). In line 2516 the authors conclude "Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer". How do the authors reach this conclusion? 1. Zero risk: The authors do not define "safe" or "adverse reaction". Without clearly stating it, the conclusion implies, that no risk is accepted "safe allergen threshold levels that would not trigger adverse reactions". In the workshop reported in Madsen et al. 2012 all stakeholder groups, including food allergic patients, agreed that if ze ro risk is expected it will not be possible to set thresholds and hence improve food allergy management. 2. Variation of published ED's: It is stated that the ED01-10 varies among publications. If appendix A is studied the only publication that gives rather different ED results is Eller et al. 2012. Eller explains that the data are historical and comes from consecutive patients and that the starting dose is relatively high which explains the high ED's. As an example 5 of 7 first dose peanut reactors underwent double blind challenge (DBPCFC) with a starting dose of 85 mg peanut. This is not described or commented by the authors. This is an example of the short comings in the discussion/argumentation in chapter 12. 3. Decision by expert committees: The authors describe that ED's vary among publication "depending" on "the decisions made by expert committees regarding the amount and characteristics of the challenge studies used, the distribution models applied, and the approach followed". This implies that th e expert committees are including data, not depending on the quality of the data, but for other reasons and that if they had chosen otherwise, the result would have been very different. The data supporting this conclusion is not presented in the opinion. 4. Patients with former severe reactions are not challenged: "that most clinicians exclude from the challenge studies those patients having the most severe reactions". This may be historical correct, but not for newer studies. The fact that the study by Eller reporting the highest ED10's includes patients that have had severe reactions and that this study in addition concludes that severe symptoms are not associated with low threshold dose is not described or commented by
12. Determination of thresholds for allergenic foods/ingredients	The Allergen Bureau Ltd	Section 12.2 line 2401 The concept of an individual threshold assumes that the sensitivity of an individual to an allergen is static and does not vary with physiological or health status or other factors. This assumption appears contrary to the evidence, from for example, wheat-dependent, exercise-induced anaphylaxis.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
12. Determination of thresholds for allergenic foods/ingredients	The Allergen Bureau Ltd	Section 12.3 line 2452 The approach to food allergen risk assessment described by Allen et al., 2014 and Taylor et al., 2014 (note both these papers were published in 2014 but are incorrectly referenced as 2013 throughout the report) has been implemented by the Allergen Bureau in Australia as the VITAL®) system since 2007 as a risk based system to guide the application of precautionary labelling of cross-contact allergens in food [http://allergenbureau.net/vital/vital]. Unlike probabilistic models of the type described by Spanjersberg et al 2007, VITAL® is a population model developed for labelling purposes. It does not involve an assessment of frequency of consumption of different foods but takes as a starting point that if the amount of allergen protein in a reference quantity of the food exceeds a defined value, precautionary labelling is relevant. Furthermore, the reference quantity of food in which the allergen protein may be present is not derived from population food consumption surveys but is dete rmined for each food product on a case-by-case basis by the food business that is using VITAL®. It intended to be representative of the amount of that food consumed on a typical eating occasion, rather than the ”serving size” identified on the label. Assumption of greater consumption increases the level of precaution inherent in the labelling advice. VITAL® is intended to be integrated as part of a company’s HACCP (Hazard Analysis Critical Control Point) based food safety program and implemented by appropriately HACCP trained food safety personnel. Threshold based Action Levels are only one element of the VITAL® system. Other tools include the VITAL® Calculator, which is a tool to assist users in recording information relevant to the VITAL® program in a consistent manner and determining potential total cross-contact levels of relevant allergens, and a comprehensive VITAL® User Guide to the system [http://allergenbureau.net/vital/vital-downloads/].
12. Determination of thresholds for allergenic foods/ingredients	The Allergen Bureau Ltd	Section 12.3 line 2494 The thresholds currently used as the basis for Action Levels in VITAL® since 2012 (VITAL® 2.0) were those recommended, by the VITAL® Scientific Expert Panel (VSEP) convened by the Allergen Bureau, using dose distribution modelling and are standardised in terms of total protein from the allergenic food as described by Allen etal 2014 Taylor et al 2014. Prior to 2012 the Action Levels were based on Lowest Observed Effect Levels (LOELS) from clinical studies as summarised by the US FDA Threshold Working Group (US FDA/CFSAN 2006), to which uncertainty factors were applied. However, this approach did not allow food manufacturers using VITAL® to characterise of the quantum of risk to the at-risk population. Action Levels used in VITAL® 2.0 are based on an eliciting dose of an allergen (EDp) at which a proportion of the allergic population (p) would be likely to react is not intended to represent a dose below which no allergic individual would react. The selection of the Eliciting Dose on which individual VITAL® Action Levels are based reflect the quality of the available data (eg the number of data points, the dose range and fit of the distribution models) rather than subjective decisions (Allen et al 2014 and Taylor et al 2014). VITAL® is a practical implementation of a threshold based labelling system underpinned by the best available data and it is anticipated that the Action Levels will be subject to continuous review in response to new data. The use of population ED values rather than individual LOELs or MOEDs enables food manufactures using VITAL® to characterise and standardise the risk associated with a decision to apply/not to apply voluntary cross-contact labelling.
12. Determination of thresholds for	The Allergen Bureau Ltd	Section 12.3 line 2498 The Voluntary Incidental Trace Allergen Labelling (VITAL®) system was launched by the Allergen Bureau in June 2007 as

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
allergenic foods/ingredients		a risk based system for precautionary labelling for the unintended presence of allergens in food, due, for example, to cross-contact during manufacturing. The goal of VITAL® is to limit the use of precautionary labelling without adequate justification through the incorporation of an allergen risk assessment step in manufacturers' HACCP based food safety programs and the use of standardized label messages. Since 2012, the VITAL® 2.0 system has used Actions Levels, based on the risk based population thresholds described by Taylor et al 2014 and Allen et al 2014. The VITAL® 2.0 grid establishes 2 Action Levels: Green (low risk; no precautionary labelling) and Yellow (possible risk; precautionary "may be present: ####" Labelling recommended). VITAL® labelling effectively enables allergic consumers and their carers to avoid purchasing foods containing cross-contact allerg ens at levels that may present a personal risk due thorough the use of standardised labelling statements.
12. Determination of thresholds for allergenic foods/ingredients	The Allergen Bureau Ltd	Section 12.4 line 2528-2530 The conclusion drawn in this part appears contradictory with the statement in line 2442 that "In food allergy, the level of exposure to allergenic foods/ingredients, which may trigger adverse allergic reactions in susceptible individuals, is extremely variable, so that setting population thresholds for allergenic foods/ingredient using a traditional toxicological risk assessment approach is not appropriate". The use of individual LOELs or MOEDs as thresholds for labelling purposes do not allow characterization of the quantum of risk represented by those thresholds. In contrast the use of statistically based populations thresholds allow a level of risk to be defined, for example ED01 being the dose at which only 1% of the allergic population are expected to react.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	General comments on section lines 2375-2530 This section covers the basis for risk assessment of allergenic foods and is therefore critical to fulfilling the terms of reference. The report describes approaches for determining both individual thresholds (based on DBPCFC) and population thresholds. Given that risk assessment is at the heart of the Panel's mandate, the expectation was that this section would contain rigorous, critical analyses of the different approaches available and their limitations, leading to a conclusion on suitability and domains of applicability. A number of issues arise with this section: Definition of terms. Elaborate on the meaning of threshold and its use in different and very distinct contexts would have been useful – Kroes et al (2000) provide a good context, which has been cited elsewhere. Researchers, clinicians and others working in this area have moved away from using the term threshold, except for individual responses, because of the high probability of confusion over dif ferent concepts (e.g. population thresholds, regulatory thresholds, management thresholds, as extensively discussed by Crevel et al (2007) and others. This section could also have provided an opportunity to define "adverse reactions". These should bear a relevance to general understanding and reference other uses. For instance, the pharmaceutical industry has standardized the criteria for adverse events. Signs and symptoms are categorised as mild, moderate, or severe, often depending upon whether the symptoms interfere with the subject's daily activities. Relatively mild symptoms are transient with no significant disruption of daily life. Using this methodology, mild symptoms and would not be classed as "adverse effects", while moderate and severe symptoms could be considered as a risk to human health. Kroes R, Galli C, Munro I, Schilter B, Würtzen G. Threshold of toxicological concern for chemical substances present in the diet: a practical tool for assessing the need for toxicity testing. Food Chem T oxicol 2000:38, 255-312. Crevel RWR, Briggs D, Hefle SL, Knulst AC, Taylor SL. Hazard characterization in food allergen risk assessment: the

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		application of statistical approaches and the use of clinical data. Food Chem Toxicol 2007; 45(5):691-701 Data analysis. The Panel's strategy and approach to the analysis of data on minimum eliciting doses (MEDs) are not easy to discern. In particular it is unclear how they have taken into account the quality of data from different sources. This is rather surprising since they explicitly mention the importance of both quality and quantity of data, thereby implying that such an analysis is required. Data quality. The Opinion comments on the variability of the ED values emanating from different studies. This issue is related to the above one of data quality and we would therefore suggest that the Panel consider critically the studies in question, rate them in terms of quality and draw transparent conclusions. This may well lead to the elimination of certain outly ing values and thereby help to resolve the issue. The Opinion mentions that decisions on selection of data are not transparent. However, at least for the peer-reviewed publications emanating from the VSEP (Allen et al 2014, Taylor et al 2014), the criteria are set out quite explicitly. These are also reiterated in Crevel et al (2014). In addition, the selection and use of data sources by the Panel is itself not completely clear: a thesis by Ben Remington is cited, but a report on the Europrevall threshold data, available publically from the UK FSA website does not seem to have been accessed.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Determination of thresholds for an individual lines 2401-2429 The Panel mention the limitations of DBPCFC, in particular the exclusion of people with a prior history of severe reactions and the variety of protocols which have been employed. Exclusion of people with a prior history is commonly cited in many publications, but the magnitude of the issue (how many people excluded out of how many tested) is not mentioned despite the fact that it is critical to quantitative risk assessment. Exclusion of people with severe reactions is almost always equated to exclusion of most sensitive individuals, even though the two terms are not synonymous. Individuals participating in DBPCFC studies that have been reported to date are rarely, if ever, a random selection of the at risk (allergic) population. Indeed the vast majority of low dose DBPCFC studies have included patients referred to specialist allergy clinics in tertiary care centres, such that the challenged population could be considered skewed towards th e more reactive/affected members of the food allergic population. The dose which provoked a severe reaction in a community (free-living) situation is usually inadequately documented. The Panel correctly comments on the variety of protocols, but does not note that since their last Opinion was published, considerable efforts have been made to harmonise protocols (Taylor et al 2004, Crevel et al 2008 and others), including many of the variables listed in Table 4 (e.g. administration protocols, form of food, etc). A considerable volume of data has been generated using these harmonised protocols or versions similar to them, thereby improving the quality of data available for dose distribution modelling. Interestingly, while the Panel mention the fact that most DBPCFCs have been conducted for diagnostic purposes rather than to establish individual thresholds, they do not mention that many of those results have been excluded from dose-distribution modelling (see 12.3) in order to avoid bias due to left-censori ng of a significant number of observations to a relatively high value. Furthermore, a similar list of shortcomings could be drawn up for classical toxicological studies, which are well-accepted as

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		a basis for risk assessment (and used regularly by other EFSA Panels), demonstrating that the available DBPCFC data can indeed be used for risk assessment. The Panel considers that the available data are insufficient for them to reach a conclusion on thresholds for any of the allergenic foods on Annex II. However, other than a brief reference to prospective studies, which could only partially address the issue, they do not provide any guidance on what they would consider sufficient
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Determination of thresholds in a population lines 2430-2503 Risk assessment approaches. The report reviews three different risk assessment approaches, as described in Madsen et al (2009): the safety assessment approach, the benchmark dose (BMD) approach and probabilistic models. Unfortunately, the Panel does not draw any conclusions regarding the suitability of particular approaches, which means that it also provides no guidance as to future directions for research and data generation.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	lines 2442-2445 On the safety/traditional risk assessment approach, the logic of the Panel's conclusion is difficult to discern. The doses to which people may react are indeed very variable, although recent studies have documented the actual range (around 6 orders of magnitude). Since the lower end of the dose distribution is now well-documented, determining a benchmark (threshold) is a textbook exercise in applying selected uncertainty factors to the NOAEL or LOAEL, depending on which is available. In determining an appropriate point of departure, the main consideration would be data quality. Madsen et al (2009) identified the main weakness in this approach, and why it is therefore not appropriate as "regulatory thresholds which are below those that can be reasonably attained in general food manufacturing, and indeed below those that could be reliably measured with current assays." lines 2446-2451 The report outlines very briefly the BMD approach, but surprisingly omits any mention of the excellent EFSA Opinion on this topic, which concluded that "the BMD approach is a scientifically more advanced method to the NOAEL approach for deriving a Reference Point, since it makes extended use of available dose-response data and it provides a quantification of the uncertainties in the dose-response data."(EFSA 2009). lines 2452-2503 Dose distribution modelling provides a useful tool for estimating thresholds for different allergens that present a common level of risk to inform population risk management decisions such as PAL. The original methodology has been published (Taylor et al 2009) and has since been used transparently by a number of research groups. All data sets are plotted as both discrete and cumulative doses, using the 3 chosen distributions (log-log, log-normal or Weibull). Various eliciting doses (eg ED01 or ED05) may be derived from each distribution providing there are a sufficient number and spread of data points. The scope for expert judgement is only used to guide the decision on a combi ned ED value, derived from the different distribution models, which weights more heavily those which provide a good fit at the lower end of the curve, to apply to risk management decisions. In the case of Taylor et al 2013 and Allen et al 2013 the resultant combined ED values were

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		specifically for application by the Allergen Bureau in Australia and New Zealand in its VITAL® 2.0 system for voluntary cross-contact labelling.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Line 2494 The Panel states (Line 2494) that there is no standard methodology to calculate population thresholds. This is correct in only a very limited way and will remain so, since the approaches described both in this Opinion and elsewhere (e.g. Madsen et al 2009) are designed to characterise the hazard, not to define a population threshold, a concept which inherently requires a judgement to be made about the acceptability of the risk. However taking a broader view, dose distribution modelling in fact uses a fairly standard methodology i.e. a BMD approach to define a point of departure (indeed one recommended by the EFSA Scientific Panel). The work of the VSEP has illustrated how apparent sensitivity to an allergen may vary on the basis of factors such as regional population, age and be affected by clinical decisions such as initial dose or choice of interim doses affecting the cumulative dose (Allen et al 2014, Taylor et al 2014 - note both these papers were published in 2014 but are incorrectly refer enced as 2013 in the report). The use of pooled data by the VSEP maximises the number of data points available, and hence the statistical power of the study. It also more closely reflects the multicultural nature of populations, minimises possible biases from patient selection or clinical protocol differences and favours a more precautionary approach by weighting the conclusions in favour of more sensitive sub-populations. As illustrated by Allen et al, at low eliciting doses, ED05 or ED01, there is little practical difference between the estimated doses from the distributions derived from different sub-populations. In relation to criticism of the use of unpublished data in dose distribution modelling, the VSEP took a procedural decision to use these data, having regard to the intended implementation of the EDs derived in the VITAL® system, and in order to maximise the number of individual data points available and hence the statistical power of the analysis. All of the unpublished data were collected fro m appropriately blinded and controlled studies undertaken in clinical centres known to the VSEP and it was used in the full expectation that it would be published by the original researchers in due course, for example Blom et al 2013. The use of unpublished data is not essential to the statistical approach used and Taylor et al 2009 have previously described the use of the same methodology using only published data for peanuts. Furthermore, it should be noted that proprietary unpublished data from animal studies, conducted according to standardised protocols and quality assurance, is commonly used in classical toxicology.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Prediction of individual sensitivity lines 2504-2514 We agree with the contents of subsection 12.4 and would point out that it has never been suggested that population thresholds should be used directly for management of food allergy at the individual level. Indeed it highlights the importance of addressing the whole issue of the safety of allergic individuals as a shared responsibility between the different stakeholders, including people with food allergies.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Conclusion lines 2515-2530 (submission comment a) The Panel concludes that “Current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer”. Since the Panel did not define “adverse reactions”, this conclusion was almost inevitable. As thoroughly describes in Section 3, clinical symptoms of food allergy

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		range from subjective (not evident to an external observer) to mild objective through to multi-organ symptoms, as in anaphylaxis. These are clearly not equivalent in terms of their impact on health or quality of life, but without a definition of adverse reaction, the Panel implicitly default to such a reaction being any effect perceived or experienced by an allergic person. This ensures that the conclusion will remain so indefinitely, since it is unlikely that any evidence can be produced that will demonstrate a No Adverse Effect Level at a population level. The likelihood that such population thresholds could not be defined was one of the main drivers for the development of the dose distribution modelling approach as discussed in Crevel et al (2007). As a consequence of not defining "adverse reactions" or "safe allergen thresholds" in a meaningful way, the Panel did not consider clearly the risk management question posed by the FSAI.
12. Determination of thresholds for allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Conclusion lines 2515-2530 (submission comment b) In rejecting the use of dose distribution modelling, in preference for the use of individual lowest lowest eliciting doses for each allergen from clinical challenge studies, the panel appears to miss the point that , these individual challenge results are: - included in the data sets used by the VSEP (Allen et al 2014, Taylor et al 2014), - generally of the same numerical order as or higher than the ED01 or ED05 lci identified by the VSEP using dose distribution modelling, - are not characterised in terms of the hazard represented nor of themselves, indicative of a specific level of risk for allergic individuals other than the individual subject tested in the challenge study. As such there is no "guarantee" that more sensitive individuals will not react at doses lower that the lowest individual LOEL reported. It is agreed that there is a need for more data on individual thresholds from clinical challenge studies for a majority of allergens of concern, however, the VSEP would also suggest that the current dose distribution modelling approach uses the best available data and provides the best available risk assessment model to inform population risk management decisions, including labelling. As new data become available, models can be revised and new ED values calculated which may lead to revised recommendations for risk management approaches, for example in regard to the conditions for application of precautionary labelling. Taken as a whole, the Panel's conclusion lacks transparency insofar as it does not naturally flow from the data and analysis in the preceding part of the section. We would submit that the Panel might like to note the parallel with classical toxicological data which are the foundation for safety assessment, as outlined below: --- Allergen assessments Study endpoints; Variability of EDs across studies; Study design; DBPCFC under standardised conditions, Exclusion of "sensitive" individuals, No prospective a ssessment; Interpretation; No interspecies extrapolation required, Adverse outcome known to be relevant; Classical toxicology Study endpoints; Different NOAELs/LOAELs etc from (animal) studies Study design; Studies conducted under standardised conditions and protocols (GLP), Young adult, healthy animals

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		(generally), No prospective evaluation possible Interpretation;Interspecies extrapolation required, Consideration of PBPK, mechanisms, Relevance of adverse outcome to man
13. Coeliac disease	AFDIAG	Comment 3 : line 2346 and after Report readers might benefit of EFSA panel scientific expertise about validation of dosage methods prior to new recipe production (matrix effect) and routine check. A analytical result only based on kit application without real validation is of no use. Comment 4 : line 2515 and after EFSA panel concludes : “current clinical, epidemiological and experimental data do not allow determining safe allergen threshold levels that would not trigger adverse reactions in a sensitised consumer”. For reasons pointed in our previous comment, thresholds are needed for quality management purposes (not necessary linked with may contain label) either as a voluntary decision of food manufacturer or as an official decision. As EFSA points that it can’t establish thresholds based on epidemiology, can it suggest other means ? For example, consumers and control bodies might take advantage of better knowledge on reality of cross contamination in food manufacturers facilities (like UE knows in animal feed production). They also might take advantage of enquiry on other countries (Switzerland, Japan, New Zealand and Australia).
13. Coeliac disease	Coeliac UK	The gluten-free diet is the medical treatment for coeliac disease. As distinct from food allergies and other food intolerances, for management of coeliac disease there is a clearly defined threshold for gluten-free labelling purposes which is both agreed internationally by Codex Alimentarius and covered by EU legislation. There is also agreed methodology for analysis of gluten levels in foods as advised by Codex Alimentarius (CCMAS).
13. Coeliac disease	European Federation of Allergy and Airways Diseases Patients’ Associations (EFA)	EFA supports European Coeliac Society which is aimed to work for the best possible safety, availability and labelling of gluten-free food advantageous for all stakeholders involved (coeliac disease patients, food sector industry and caterers).Currently there are many products where stickers “gluten free” “may contain gluten” and “non-suitable for coeliac person” are used simultaneously.We also see more and more “gluten free” stickers on products that are not containing naturally gluten and, thus, have no right to say that. We can imagine that in the future, we will find more and more products saying free from but with no regulation. What is more,”gluten free” mode is often driven not by coeliac disease awareness but is used as a market opportunity for food production based on threshold.
13. Coeliac disease	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
13. Coeliac disease	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define “high temperature” for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – “Almonds are not nuts…” a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo ‘DBPCFC’ not ‘DBPCFG’ • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
13. Coeliac disease	Italian Coeliac Association	Lines 2720 and 2761 we suggest to change the statements between brackets: “…oats (because oats is commonly contaminated by other grains and some oats cultivars have been showed in vitro to be toxic in CD).." in alignement with lines 2593 - 2597.
13. Coeliac disease	na	Any food containing gluten or products that are derived from grains such as wheat should be labelled in the allergy box every time. EVEN IF THE ITEM IS GLUCOSE SYRUP, STARCH, OR SUGAR. Gluten free should mean there is 0 ppm gluten. Low gluten should mean less than 20ppm Contains gluten, should mean it contains more than 20ppm gluten. The word "free" means zero in every other context. Alcohol free, does not mean just "a little bit" for example. In a sugar drink like lemonade for example, there are a lot of parts, and even a low ppm therefore a lot of gluten molecules in a glass!

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		I discovered that "glucose syrup" is often sugar from a wheat source, but is sometimes labelled as "sugar". Sugar should mean from sugar beet. Glucose syrup should always have a note of the source in brackets afterwards. eg Glucose syrup, (from wheat). having discovered this, fellow coeliac are discovering why they cannot avoid gluten, and why they continue to get ill, even on a strict diet. Because the labelling when the product may contain sugars is exempt and therefore useless. Even gluten free is useless as this is defined as 20ppm or less, useless if you react to less than 20ppm gluten as so many do. Just because 50% of coeliacs do not noticeably react to 20ppm gluten, does not mean it is not poisoning the other 50% and doing them serious harm! You would not disagree if it affected you. Given how serious the potential consequences are, this needs urgent action. The food industry should not levy commercial pressures on those making these decisions, they should be able to trace and control their production. Gluten can be tested to 1ppm now, no excuse.
13. Coeliac disease	R-Biopharm AG	2580-2589 Not only wheat contains gluten. Rye and barley contain secalin, hordeins and specials glutelins 2612 Cite more papers since more are available 2626 An international collaborative study (Immer AOAC OMA JAOAC Vol 95 No. 4 2012) has been carried out using the R5 Elisa, the method is now official method of Analysis (http://eoma.aoac.org/) 'Gliadin as a measure of Gluten I Foods containg wheat, rye and barley Enzyme Immoassay Method based on s specific monoclonal antibody R5. (The older AOAC method using the Skerritt antibody 401/21 mAb is less sensitive than the R5 method and therefore out of date. Recently two additional collaborative studies have been carried out. The first with the R5 sandwich ELISA (Koehler AACCI collab study R5 Sandwich ELISA CFW-58-1-0036 (2)) and the second with the R5 competitive ELISA (Koehler AACCI R5 competitive ELISA CFW-58-3-0402). The AACC has now adopted both methods as official AACCI standards. The competitive R5 ELISA which has been validated uses an ethanol extr action (and not a UPEX extraction). 2636 There is another monoclonal antibody used for the detection of gluten, the G12, please mention it. 2653 Mention the collaborative tests with the different systems e.g. under the control of AACC or AOAC. 2656 The Paper of Diaz-Amigo and Popping is bias and driven by a commercial idea to sell LC-MS/MS methods of their company (Eurofins) 2657 Describe the LFD as detailed as the biosensors. Recently a collaborative study using the R5 dip stick has been carried out within an AOAC validation programme. 2679 change to mg/kg 2692 State the LOD of the method and the amounts present in beer 2697-2714 Shorten, because according to CODEX you need to measure proteins

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		2738 The CODEX Standard 118-1979 specifies limit values for gluten-free food and also on page 3 in the last sentence the method that should be used for the determination of gluten: "Enzyme-linked Immunoassay (ELISA) R5 Mendez method." 2748 Include the FDA and Health Canada regulations
14. Allergy to cereals containing gluten	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
14. Allergy to cereals containing gluten	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
14. Allergy to cereals containing gluten	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
14. Allergy to cereals containing gluten	na	Any food containing gluten or products that are derived from grains such as wheat should be labelled in the allergy box every time. EVEN IF THE ITEM IS GLUCOSE SYRUP, STARCH, OR SUGAR. Gluten free should mean there is 0 ppm gluten. Low gluten should mean less than 20ppm

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Contains gluten, should mean it contains more than 20ppm gluten. The word "free" means zero in every other context. Alcohol free, does not mean just "a little bit" for example. In a sugar drink like lemonade for example, there are a lot of parts, and even a low ppm therefore a lot of gluten molecules in a glass! I discovered that "glucose syrup" is often sugar from a wheat source, but is sometimes labelled as "sugar". Sugar should mean from sugar beet. Glucose syrup should always have a note of the source in brackets afterwards. eg Glucose syrup, (from wheat). having discovered this, fellow coeliac are discovering why they cannot avoid gluten, and why they continue to get ill, even on a strict diet. Because the labelling when the product may contain sugars is exempt and therefore useless. Even gluten free is useless as this is defined as 20ppm or less, useless if you react to less than 20ppm gluten as so many do. Just because 50% of coeliacs do not noticeably react to 20ppm gluten, does not mean it is not poisoning the other 50% and doing them serious harm! You would not disagree if it affected you. Given how serious the potential consequences are, this needs urgent action. The food industry should not levy commercial pressures on those making these decisions, they should be able to trace and control their production. Gluten can be tested to 1ppm now, no excuse.
14. Allergy to cereals containing gluten	R-Biopharm AG	2909 Avenin is still under discussion if it can be potential dangerous for coeliacs
14. Allergy to cereals containing gluten	The Allergen Bureau Ltd	Section 14.7 line 3088 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified wheat thresholds from 40 individuals (37 published and 3 unpublished), comprising: 28 children and 12 adults; 5 left-censored and 1 right-censored. Overall, the wheat data set was considered to be sufficient for dose distribution modelling and to support an estimate of ED values. On the basis of the VSEP recommendation, the Reference Dose for VITAL® 2.0 is set at 1.0 mg wheat protein, consistent with the 95% lower confidence interval of the ED05 values of all three distributions based on discrete and cumulative doses for adults and children (Allen et al 2014, Taylor et al 2014). The VSEP noted that wheat-allergic consumers would be largely protected by foods containing <20 ppm gluten.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
14. Allergy to cereals containing gluten	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
15. Allergy to milk and dairy products	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
15. Allergy to milk and dairy products	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
15. Allergy to milk and dairy products	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
15. Allergy to milk and dairy products	FoodDrinkEurope	Section 15.5.2. (lines 3413-3418) • The paragraph on hydrolysis is limited and attention is drawn to the comments on hydrolysis given on section 10.
15. Allergy to milk and dairy products	FoodDrinkEurope	15.8 Conclusion (for milk) (lines 3560 – 3562) • With regards to the phrase: "Milk is a common cause of allergic reactions in childhood", we would like to state that the phrase in incorrect and the percentage is given later in the text (1-0,5 %). Milk is also a too broader concept, and bovine milk protein would be more correct. So we propose to either delete the sentence or change the text.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
15. Allergy to milk and dairy products	Food & Drink Federation	Section 15.5.2. (lines 3413-3418) • The paragraph on hydrolysis is limited and attention is drawn to the comments on hydrolysis given in section 10.
15. Allergy to milk and dairy products	Food & Drink Federation	Section 15.8 Conclusion (for milk) (lines 3560 – 3562) • With regards to the phrase: "Milk is a common cause of allergic reactions in childhood", we would propose that the text is amended or deleted. This is based on the fact that the percentage stated is 1-0,5% and that milk is too broad a concept.
15. Allergy to milk and dairy products	R-Biopharm AG	3460 competitive is NOT the most used format! This information is wrong at all. In most cases sandwich ELISA are used. There are milk ELISAs available based on BLG and Casein antibodies since BLG and Casein are allergenic milk proteins 3465 Also cite the paper of Johnson et al. (2014 in Food Chemistry; see above) 3508 Also cite Lacorn et al. (2014 in Food Anal Meth 7:417-429)
15. Allergy to milk and dairy products	The Allergen Bureau Ltd	Section 15.7 line 3521 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified milk thresholds from 351 individuals (222 published studies and another 129 unpublished), comprising: 323 children, 25 adults and 3 of undetermined age; 59 left-censored and 19 right-censored. Overall, the milk data set was considered to be excellent. On the basis of the VSEP recommendation, the Reference Dose for VITAL® 2.0 is set at 0.1 mg milk protein, based on the ED01 values of the log normal and log logistic distributions based on discrete and cumulative doses for both adults and children (Allen et al 2014, Taylor et al 2014)
15. Allergy to milk and dairy products	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
15. Allergy to milk and dairy products	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Allergy to milk and dairy products. Lines 3521-3571. The publication of Patriarca et al 2002 was not included, though this publication has information on MOED. Oral desensitisation in... [Int J Immunopathol Pharmacol. 2002 Jan-Apr] - PubMed - NCBI

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Page 81 Consistency in using a specific reference or excluding it is not present in the Scientific Opinion. For example the reference of Blom et al 2013 with information on MOEDs of 7 major allergens is included for the evaluation of cashew nut, milk, peanut and egg, however the threshold doses for soy, walnut and hazelnut are not part of the evaluation of these allergenic foods.
16. Allergy to eggs	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
16. Allergy to eggs	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
16. Allergy to eggs	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define “high temperature” for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – “Almonds are not nuts…” a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo ‘DBPCFC’ not ‘DBPCFG’ • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
16. Allergy to eggs	Interest Group on Food Allergy - Sociedade Portuguesa Alergologia Imunologia Clinica	Line 3609, page 83: This difference is not explained. I would suggest you add the bibliographic reference. Line 3676, page 84: I would suggest you add "breast milk" as other route of egg sensitisation.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
16. Allergy to eggs	International organisation of vine and wine (OIV)	Paragraph 16.5.4.2 Under Regulation (EU) No. 579/2012 in conjunction with Regulation (EU) No. 1234/2007 article 120g and the OIV guidelines 502/2012 based on 427/2010 there exists an analytical threshold for casein and ovalbumin in wine at 0.25mg/L. Wines treated with casein or ovalbumin products and proven beyond this limit of 0.25mg/L have not to be labeled with egg or milk. The Members states of the OIV will consider for adoption, at the next General Assembly in November 2014, a Code of good fining practices for wine to be applied in the use of proteinaceous allergenic wine fining agents (casein and egg white). In these guidelines, it is mentioned that fining involves the addition of absorbent/adsorbent or reactive material to must or wine in order to reduce or eliminate the presence of certain less desirable components. Fining agents are added to modify a wine's clarity, colour, texture or flavour and especially to ensure a wine remains in a particular stable state for the longest possible period of time. The fining process is designed so that the fining agents added do not remain in the musts or wines that have had to be fined. In these guidelines, it is also recognized in particular best practice filtration methods (including fine filtration using diatom powder and cellulose fibres and/or pre-bottling filtration through a 0.65 µm or smaller membrane filter, or performing treatments of equivalent effect) should be used to remove insoluble protein fining agents. If the treated wine is simply racked off the lees remaining from the fining treatment and bottled without filtration, or if a less rigorous filtration or other technique for removal of the lees is applied, an analysis must always be conducted prior to bottling. However, even in the case of filtration, it is recommended to analyse filtered or unfiltered wines to confirm that no residual fining agent(s) can be detected. Paragraph 16.6.4 For the analysis of egg proteins in wine ELISA and mass spectrometry (MS) methods are presented. Already in these sections concerning the wine the cited limits of detection (LOD) clearly show that the immunological method ELISA still is the most sensitive method. This is supported at the beginning in the Summary of the opinion and in Chapter 11. "MS methods for quantitative analysis based on specific standard peptides or stable isoptope labelling are not yet suitable for analyses of large numbers of samples, but can confirm results obtained otherwise." Beside the less sensitive LOD of MS than of ELISA in most cases furthermore MS is not able to detect the allergenic potency of the protein, the still intact epitope of the allergenic protein, what is done with ELISA.
16. Allergy to eggs	R-Biopharm AG	3893 The author used an egg-white assay with a cross-reactivity of about 10% to quantify lysozyme. This paper is biased due to the fact that the assay was not used as recommended. Please delete. 3905 Also cite Lacorn et al. (2011 in Am. J. Enol. Vitic. 62:382 ff) and Lacorn et al. (2014 in Food Anal Meth 7:417-429)
16. Allergy to eggs	The Allergen Bureau	Section 16.7 line 3931

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
	Ltd	The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified egg thresholds for 206 individuals (110 published and 96 unpublished), comprising: 174 children, 12 adults, and 20 of undetermined age; 24 left-censored and 33 right-censored. Overall, the egg data set was considered to be excellent. The data set pooled data for both raw and cooked eggs. On the basis of the VSEP recommendation, the Reference Dose for VITAL® 2.0 is set at 0.03 mg egg protein consistent with the ED01 and 95% lower confidence interval of the ED05 values of the Weibull and other distributions and based on discrete and cumulative doses for children (Allen et al 2014, Taylor et al 2014).
16. Allergy to eggs	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
16. Allergy to eggs	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Allergy to egg (hen's egg) Lines 3931-3967. The publication of Meglio et al 2013 was not included Oral food desensitization in children... [Pediatr Allergy Immunol. 2013] - PubMed - NCBI. Pg. 90 Consistency in using a specific reference or excludin g it is not present in the Scientific Opinion. For example the reference of Blom et al 2013 with information on MOEDs of 7 major allergens is included for the evaluation of cashew nut, milk, peanut and egg, however the threshold doses for soy, walnut and hazelnut are not part of the evaluation of these allergenic foods.
17. Allergy to nuts	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
17. Allergy to nuts	FEDIOL	We note that the discussion on Minimum Eliciting Doses does not seem to refer to recent studies, some of which are cited in other parts of the Opinion. The section does not address the risk from exposure to different tree nuts and their derived products in terms of its potential public health impact.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		However, it should be noted that exemptions have been given in the past on the subject. For example, see Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from CEPS on nuts used in distillates for spirits pursuant to Article 6 paragraph 11 of Directive 2000/13/EC, as adopted on 3 May 2007. The opinion states that "Based on the data submitted by the applicant, the Panel notes that proteins and peptides are not carried over into the distillate during a properly controlled distillation process, at least not in amounts above 1 mg/L. Although the analytical evidence is derived from experiments that were performed predominan tly with almonds, the Panel considers that distillates made from nuts are unlikely to trigger a severe allergic reaction in susceptible individuals." We would also like to mention that lines 4536-4538 suggest that the cited papers demonstrate reactivity to hazelnut at levels where it is undetectable. However, having looked at those papers, they refer to DBPCFC studies in which known, documented amounts of hazelnut were given to study participants. Given that the Opinion is likely to be highly cited, we believe that this should be clarified in the final opinion.
17. Allergy to nuts	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
17. Allergy to nuts	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways'

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define “high temperature” for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – “Almonds are not nuts…” a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo ‘DBPCFC’ not ‘DBPCFG’ • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
17. Allergy to nuts	R-Biopharm AG	4390 the RIDASCREEN FAST Hazelnut ELISA is accepted as a DIN CEN/TS 15633-2:2013 method. 4520 Also multiplex PCR for the quantification of Peanut/Hazelnut/Walnut available (4plex PCR R-Biopharm).
17. Allergy to nuts	The Allergen Bureau Ltd	Section 17.7 line 4535 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified hazelnut thresholds were obtained for 202 individuals (29 published and 173 unpublished), comprising: 61 children and 141 adults; 4 left-censored and 67 right-censored. Overall, the hazelnut data set was considered to be good but would be enhanced by publication of the unpublished data. The VSEP recommended that the Reference Dose for VITAL® 2.0 be set at 0.1 mg hazelnut protein, based on the ED01 and 95% lower confidence interval of the ED05 values of the log logistic and other distributions and also on discrete and cumulative doses for adults and children (Allen et al 2014, Taylor et al 2014). Cashew thresholds were obtained for 31 children (all unpublished); 1 left-censored and 16 right-censored. Overall, the data set was considered to be marginally sufficient for dose distribution modelling and to support an estimate of ED values. The VSEP recommended a provisional Reference Dose for VITAL® 2.0 of 2.0 mg cashew protein, consistent with the 95% lower confidence interval of the ED05 values of all three distributions based on discrete and cumulative doses for children (Allen et al 2014, Taylor et al 2014). In view of the limited data set for cashew and the paucity of data for other tree nuts, the ED value for hazelnut was used to set a Reference Dose of 0.1mg for all tree nuts in VITAL® 2.0
17. Allergy to nuts	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
17. Allergy to nuts	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to,

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Allergy to nuts. Lines 4535-4564. Here the publication of Blom et al 2013 is referred to for the MEDs on cashew nut, however it is not clear why the information on walnut and hazelnut in that same publication is not included for evaluation of allerg y to nuts. Threshold dose distributions for 5 ma... [J Allergy Clin Immunol. 2013] - PubMed - NCBI The study of Flinterman et al 2006 with a large number of individual MEDs on hazelnut is not included (Clinical reactivity to hazelnut in ch... [J Allergy Clin Immunol. 2006] - PubMed - NCBI Further the data for hazelnut and cashew nut are combined, however the rationale to combine the threshold dose information for the different nuts is not made clear. Pg 105 Consistency in using a specific reference or excluding it is not present in the Scientific Opinion. For example the reference of Blom et al 2013 with information on MOEDs of 7 major allergens is included for the evaluation of cashew nut, milk, peanut and egg, however the threshold doses for soy, walnut and hazelnut are not part of the evaluation of these allergenic foods. Lines 4256-4258 This statement is false and relies on extremely old literature for nuts. It has been shown multiple times that nuts other than hazelnut (and an extremely hig h number of other foods) can have reactions induced by pollen-mediated food sensitization.
18. Allergy to peanuts	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature. For example section 18.5.6 re peanut oil does not cite Hourihane et al (Randomised, double blind, crossover challenge study of allergenicity of peanut oils in subjects allergic to peanuts BMJ. 1997 Apr 12;314(7087):1084-8.).
18. Allergy to peanuts	FEDIOL	The draft opinion has not updated the analysis on the risk posed by exposure to very small amounts of peanut, despite the vast amount of peanut challenge data now available in the public domain, including data from highly sensitive and well-characterised peanut-allergic individuals (Taylor et al 2009, 2010). We also notice that the review by Moneret-Vautrin (Moneret-Vautrin D. A., Kanny G. Update on threshold doses of food allergens: implications for patients and the food industry. Curr. Opin. Allergy Clin. Immunol.2004, 4: 215-219), addressing the allergenicity of refined peanut oil has not been taken into account. However, the review highlighted that no reactions to refined peanut oil had been observed since the introduction of a FEDIOL Code of Practice on refining We would also highlight that no evidence has emerged to contradict the observations in that review in the 10 years since it was published.
18. Allergy to peanuts	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
18. Allergy to peanuts	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
18. Allergy to peanuts	FoodDrinkEurope	• Section 18.5.1 Thermal processing, lines 4766-4788 The point about the evidence which suggests a difference in the allergenicity of roasted versus boiled peanuts is of academic interest, but in practical terms it has no utility in Europe. There are no boiled peanuts in this market, as far as we are aware, and consuming peanuts in this manner is not part of any EU Member State's snacking culture.
18. Allergy to peanuts	Food & Drink Federation	Section 18.5.1 Thermal processing, lines 4766-4788 The point about the evidence which suggests a difference in the allergenicity of roasted versus boiled peanuts is of interest, but has no relevance in Europe. As far as we are aware, there are no boiled peanuts in this market, and the consumption of peanuts treated in this manner is not part of any EU Member State's snacking culture.
18. Allergy to peanuts	The Allergen Bureau Ltd	Section 18.7 line 5002 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified peanut thresholds were obtained for 750 individuals (489 published and 261 unpublished), comprising: 584 children, 99 adults, and 67 of undetermined age; 30 left-censored and 132 right-censored. The peanut data set was considered to be excellent. On the basis of the VSEP recommendation, the Reference Dose for VITAL® 2.0 is set at 0.2 mg peanut protein, based on the ED01 values of the log normal and log logistic distributions for discrete and cumulative doses for both adults and children at (Allen et al 2014, Taylor et al 2014).
18. Allergy to	The iFAAM FP7	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
peanuts	Project	systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
18. Allergy to peanuts	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Pg. 116 Consistency in using a specific reference or excluding it is not present in the Scientific Opinion. For example the reference of Blom et al 2013 with information on MOEDs of 7 major allergens is included for the evaluation of cashew nut, milk, p eanut and egg, however the threshold doses for soy, walnut and hazelnut are not part of the evaluation of these allergenic foods. Lines 5060-5062 The use of highly sensitive is confusing here as sensitivity describes the MED/MOED of an allergic individual and severity is a separate issue. Highly sensitive peanut individuals with MOEDs <100µg peanut protein have been shown to have mild symptoms. Severe reactors by history were shown by Taylor et al 2010 to have the same MOED sensitivity and subsequent ED values as non-severe reactors by history. Lines 5072-5074 The Scientific Opinion states “Few data are available on the doses which may trigger allergic reactions in highly sensitive patients, who are often excluded from challenge tests but tend to react to lower doses than patients with mild symptoms.” The term “highly sensitive” is used incorrectly as the individuals with the most sensitive MOED do not necessarily have severe symptoms. Patients with history of anaphylaxis have been excluded from challe nge by some past studies. However, clinical data does exist from centers that do not exclude severe reactors by history (Taylor et al 2010, Blom et al 2013). Taylor et al 2010 showed that no difference in ED values occurred when comparing patients with and without a history of severe allergic reactions to peanut. In fact, patients with severe histories have been shown to have similar symptoms as patients with non-severe histories during low dose threshold challenges. Ch 19 (5512-5514) states the issue of excluding patients with severe reaction history correctly as follows “However, few data are available on the doses which may trigger allergic reactions in patients with anaphylactic reactions to soy, which were often excluded from challenge tests,...”
19. Allergy to soy	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		literature.
19. Allergy to soy	FEDIOL	Whilst this section explains in details the allergenicity of soy, it does not refer in section 19.5.4.2 (lines 5294 to 5306) to the EFSA opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from FEDIOL and IMACE on fully refined soybean oil and fat pursuant to Article 6, paragraph 11 of Directive 2000/13/EC- for permanent exemption from labelling, as adopted on 15 October 2007. The Opinion however states that with the process by which soybean oils are neutralised (alkali refined) bleached and deodorised (N/RBD), it is not very likely that such N/RBD soybean oils will trigger a severe allergic reaction in susceptible individuals under the conditions of production and use. This led to the permanent exemption of labelling under Directive 2003/13 and under Regulation 1169/2011 of fully refined soybean oil and fat and products thereof, "insofar as the process that they have undergone is not likely to increase the level of aller genicity assessed by EFSA for the relevant product from which they originated". FEDIOL trusts that this should be added to the section 19.5.4.2. Another good example is the evaluation of tocopherols from soya under the same procedure. The EFSA opinion in this case was "Considering the information provided by the applicant regarding the starting material, the subsequent production process, and the demonstration of low residual protein content, the Panel considers that it is unlikely that natural mixed tocopherol/D-alpha tocopherols from soybean sources will trigger a severe allergic reaction in susceptible individuals." (Opinion of the Scientific Panel on Dietetic Products, Nutrition and Allergies on a request from the Commission related to a notification from Cognis, ADM and Cargill on natural mixed tocopherols (E306), natural D-alpha tocopherol, natural D-alpha tocopherol acetate and natural D-alpha tocopherol succinate from soybean sources pursuant to Article 6, paragraph 11 of Directive 2000/13/EC, as adopted on 3 May 2007). FEDIOL trust that this should also be added to section 19. These are excellent illustrations of the situation where processing reduces the protein content of the original allergenic source to such an extent that the amount remaining poses a negligible risk, and thereby also underlines the power of quantitative risk assessment, as well as its feasibility. For exhaustivity, it should also be mentioned that 2 other opinions lead to a permanent exemption for Vegetable oils derived phytosterols and phytosterol esters from soybean sources and Plant stanol ester produced from vegetable oil sterols from soybean sources by respectively 2 EFSA opinions taken in 2007.
19. Allergy to soy	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
19. Allergy to soy	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
19. Allergy to soy	R-Biopharm AG	5360 The DLA (http://www.dla-lvu.de/) carries out proficiency testing for laboratories. In the DLA round carried out in 2013-02 'Soja and Wheat in „gluten free" Pastry' was analyzed. The sample used contained heat treated soy. Of the participating labs several used RIDASCREEN®FAST Soya which was able to detect soya in the heat treated food. Also the Paul Ehrlich Institute in Langen has carried out research on different soya ELISA kits which is going to be published.
19. Allergy to soy	The Allergen Bureau Ltd	5438 19.7 Soy - Minimal (observed) eliciting doses Section 19.7 line 5438 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified soybean thresholds for 80 individuals (43 individuals published and 37 unpublished), comprising: 33 children, 25 adults, and 22 of undetermined age; 6 left-censored and 28 right-censored. Overall, the soybean data set was considered to be sufficient. The VSEP observed that some challenge studies with soy flour indicate reasonably high individual soybean thresholds, whereas studies using soy milk with subjects selected on the basis of a history of adverse reactions to a particular brand(s) of soy milk appear to have indicated lower individual thresholds. On the basis of the VSEP recommendation, the Reference Dose for VITAL® 2.0 is set at 1.0 mg soybean protein, consistent with the 95% lower confidence interval of the ED05 values of the log normal and other distributions based on discrete and

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		cumulative doses for children and adults having soy flour challenges (Allen et al 2014, Taylor et al 2014)). The VSEP noted that this level may not completely protect certain individuals sensitive to specific brands of soy milk.
19. Allergy to soy	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
19. Allergy to soy	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
19. Allergy to soy	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Pg. 125 Consistency in using a specific reference or excluding it is not present in the Scientific Opinion. For example the reference of Blom et al 2013 with information on MOEDs of 7 major allergens is included for the evaluation of cashew nut, milk, peanut and egg, however the threshold doses for soy, walnut and hazelnut are not part of the evaluation of these allergenic foods. Lines 5443-5466 Magnolfi et al 1996, Zeiger et al 1999, and Fiocchi et al 2003 used Isomil or Multisoy infant formulas NOT soy milk during challenges. Due to heavier processing, soy in infant formula will be closer in form to soy flour than a whole bean filtered soy milk.
20. Allergy to fish	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
20. Allergy to fish	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
20. Allergy to fish	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
20. Allergy to fish	FoodDrinkEurope	20.2.1.2 (lines 5673-5675) • A statement is made regarding the severity of reactions to mammalian collagen but no references provided.
20. Allergy to fish	Food & Drink Federation	Section 20.2.1.2 (lines 5673-5675) • A statement is made regarding the severity of reactions to mammalian collagen but no references are provided.
20. Allergy to fish	The Allergen Bureau Ltd	Section 20.7 line 5888 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified fish thresholds were obtained for 19 individuals (15 published and 4 unpublished), comprising: 18 adults and 1 child; 6 left-censored and 2 right-censored. The data set covered challenges with several different fish species, including cod (10), catfish (5), snapper (1), halibut (1), tuna (1), and tilapia (1). The fish data set was considered as insufficient for dose distribution modelling or to allow an estimate of ED values. In view of the lack of data sufficient to allow the estimation of ED values for fish, the previous VITAL® Action Level of 0.1 mg fish protein was retained. This value was based on the LOEL from clinical studies reported by the US FDA Threshold Working Group (US FDA/CFSAN 2006) with a 10 fold uncertainty factor applied.
20. Allergy to fish	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
20. Allergy to fish	TNO - Nederlandse	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
	Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Allergy to fish Lines 5888-5908. The Scientific Opinion does state if the minimum reaction in Hansen and Bindslev-Jensen 1992 to 6 mg codfish is subjective or objective, or if the 6 mg is 6 mg codfish or 6 mg protein. Remington et al reports a cumulat ive MOED of 10.2 mg protein (discrete 9.15 mg protein) as the minimum objective reaction from this same study. Lines 5895-5897 The Scientific Opinion states “Few data are available on the doses which may trigger allergic reactions in highly sensitive patients, who are often excluded from challenge tests but tend to react to lower doses than patients with mild symptoms.” The term “highly sensitive” is used incorrectly as the individuals with the most sensitive MOED do not necessarily have severe symptoms. Patients with history of anaphylaxis have been excluded from challenge by some past studies. However, clinical data does exist from centers that do not exclude severe reactors by history (Taylor et al 2010, Blom et al 2013). Taylor et al 2010 showed that no difference in ED values occurred when comparing patients with and without a history of severe allergic reactions to peanut. In fact, patients with severe histories have been shown to have similar symptoms as patients with non-severe histories during low dose threshold challenges. Ch 19 (5512-5514) states the issue of excluding patients with severe reaction history correctly as follows “However, few data are available on the doses which may trigger allergic reactions in patients with anaphylactic reactions to soy, which were often excluded from challenge tests,”
21. Allergy to crustaceans	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
21. Allergy to crustaceans	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
21. Allergy to crustaceans	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments?

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
21. Allergy to crustaceans	R-Biopharm AG	6209 Also other commercially available Lateral flow tests available!!! (e.g. R-Biopharm) Please check carefully.
21. Allergy to crustaceans	The Allergen Bureau Ltd	Section 21.7 line 6266 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified shrimp thresholds were obtained for 48 adults (25 published and 23 unpublished) ; 26 right-censored and none left-censored. Overall, the shrimp data set was considered as marginally sufficient for dose distribution modelling and to support an estimate of ED values. On the basis of the VSEP recommendation the Reference Dose for VITAL® 2.0 is set at 10 mg shrimp protein, consistent with the 95% lower confidence interval of the ED05 values of the three distributions based on discrete and cumulative doses for adults (Allen et al 2014, Taylor et al 2014).
21. Allergy to crustaceans	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
21. Allergy to crustaceans	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		- the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Allergy to crustaceans lines 6266-6279. More information on the allergy to shrimp is public available in the abstract of Nordlee et al 2013 Threshold Dose for Shrimp... [J Allergy Clin Immunol 2013] - PubMed - NCBI and Atkins et al 1985 Evaluation of immediate adverse reactions... [J Allergy Clin Immunol. 1985] - PubMed - NCBI
22. Allergy to molluscs	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
22. Allergy to molluscs	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
22. Allergy to molluscs	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define “high temperature” for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – “Almonds are not nuts…” a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo ‘DBPCFC’ not ‘DBPCFG’ • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra “Bernhisel-Broadbent” from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		sulphites due to fermentation.
22. Allergy to molluscs	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
23. Allergy to celery	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
23. Allergy to celery	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
23. Allergy to celery	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
23. Allergy to celery	The Allergen Bureau Ltd	Section 22.7 line 6659 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified celery thresholds for 39 individuals (12 published and 27 unpublished), comprising: 27 adults and 12 of undetermined age; 15 left-censored and 4 right-censored. The celery data set was considered as insufficient to allow an estimate of ED values.
23. Allergy to celery	The iFAAM FP7	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
	Project	systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
23. Allergy to celery	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy
23. Allergy to celery	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy
24. Allergy to lupin	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
24. Allergy to lupin	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
24. Allergy to lupin	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this?

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
24. Allergy to lupin	The Allergen Bureau Ltd	Section 23.7 line 6894 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified lupin thresholds for 24 individuals (9 published and 15 unpublished). Comprising: 9 children and 15 adults; 2 left-censored and 7 right-censored. Overall, the data set was considered as sufficient for dose distribution modelling and to support an estimate of ED values On the basis of the VSEP recommendation, the Reference Dose for VITAL® 2.0 is set at 4.0 mg lupin protein, consistent with the 95% lower confidence interval of the ED05 values of the log normal and log logistic distributions based on discrete and cumulative doses for children and adults (Allen et al 2014, Taylor et al 2014).
24. Allergy to lupin	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
24. Allergy to lupin	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy
25. Allergy to sesame	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
25. Allergy to sesame	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
25. Allergy to sesame	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments?

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
25. Allergy to sesame	The Allergen Bureau Ltd	Section 24.7 line 7133 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified sesame seed thresholds for 21 individuals (all published), comprising: 6 children, 13 adults, and 2 of undetermined age.; 2 left-censored and 1 right-censored. Overall, the sesame seed data set was considered as marginally sufficient for dose distribution modelling and to support an estimate of ED values. On the basis of the VSEP recommendation the Reference Dose, for VITAL® 2.0 is set at 0.2 mg sesame seed protein, consistent with the 95% lower confidence interval of the ED05 values of the three distributions based on discrete and cumulative doses for children and adults (Allen et al 2014, Taylor et al 2014).
25. Allergy to sesame	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
25. Allergy to sesame	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		Details For the above comments examples are found throughout the evaluation in the sections and are summarized, but not limited to, Allergy to sesame Lines 7133-7149. In a lack of consistency, the dissertation of Remington 2013 was referenced when summarizing available MOED data for other allergens but not for sesame and multiple other allergens. More information and more sensitiv e MOED data is available from Morisset et al 2003 for sesame Thresholds of clinical reactivity to milk, egg, peanut and sesame... [Clin Exp Allergy 2003] - PubMed - NCBI and multiple other publications by the same group.
25. Allergy to sesame	Università del Piemonte Orientale A. Avogadro, Italy (Institution ex art 36 recognised by EFSA)	25.2.5. Factors affecting prevalence of sesame allergy Please consider to insert: A study (based on the evaluation the sensitization profiles of 18 Italian individuals who experienced clinical symptoms after sesame seed consumption, including 4 anaphylactic reactions) confirmed the 11S globulin as the prevalent and almost exclusive reactive protein of the sesame. This study shed light on the active role of the basic subunit of this globulin family. The limited accessibility of this polypeptide chain, unless the interchain disulphide bonds are cleaved, may be one of the reasons for its structural/functional stability and, thus, confirming the high IgE reactivity. (Ref. Ann Allergy Asthma Immunol. 2010 Dec;105(6):458-64. doi: 10.1016/j.anai.2010.10.001. Molecular insight into IgE-mediated reactions to sesame (Sesamum indicum L.) seed proteins. Magni C1, Ballabio C, Restani P, Fuggetta D, Alessandri C, Mari A, Bernardini R, Iacono ID, Arlorio M, Duranti M.)
26. Allergy to mustard	EAACI	This chapter would have benefited from having taken a systematic approach and applied a grading system for undertaking a quality assessment of the data available under the different sub headings. As it stands the chapter is incomplete and missing literature.
26. Allergy to mustard	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
26. Allergy to mustard	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
26. Allergy to mustard	The Allergen Bureau Ltd	Section 25.7 line 7387 The Allergen Bureau VITAL® Scientific Expert Panel (VSEP) identified mustard thresholds for 33 individuals (all published), comprising: 9 children, 9 adults, and 15 of undetermined age; 2 left-censored and 10 right-censored. Overall, the data set was considered as sufficient for dose distribution modelling and to support an estimate of ED values. On the basis of the VSEP recommendation the Reference Dose for VITAL® 2.0 is set at 0.05 mg mustard protein, consistent with the 95% lower confidence interval of the ED05 values of all three distributions based on discrete and cumulative doses for children and adults (Allen et al 2014, Taylor et al 2014).
26. Allergy to mustard	The iFAAM FP7 Project	These chapters provide a review of the literature on a food-by-food basis. This does not seem to have been performed using a systematic approach and lacks the rigour of that approach. The EFSA Opinion would have benefited from the approach taken by EAACI in putting together the Food Allergy Guidelines.
26. Allergy to mustard	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Related to our expertise our comments and suggestions are linked to the evaluation of the sensitivity of allergic individuals for different allergenic foods. Overall for the paragraphs describing the evaluation of the sensitivity of allergic individuals : - it is not clear how the literature search was performed, as the search words used and the quality criteria to include or exclude specific publications are not mentioned. - the criteria used to include or exclude publications is not consistent. - the approach of how the evaluation is reported shows a lack of consistency, for example see the evaluation of peanut and soy
27. Adverse reactions to sulphites	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
27. Adverse reactions to sulphites	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma. • Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum. • Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
27. Adverse reactions to sulphites	FoodDrinkEurope	Section 27: The following reference should be considered: Corder EH and Buckley CE (1995) J Clin Epidemiol 48, 1269. Aspirin, salicylate, sulfite and tartrazine induced bronchoconstriction. Safe doses and case definition in epidemiological studies.
27. Adverse reactions to sulphites	Food & Drink Federation	Section 27: The following reference should be considered: Corder EH and Buckley CE (1995) J Clin Epidemiol 48, 1269. Aspirin, salicylate, sulfite and tartrazine induced bronchoconstriction. Safe doses and case definition in epidemiological studies.
27. Adverse reactions to sulphites	The Allergen Bureau Ltd	Section 26.8 line 7746 The Australia New Zealand Food Standards Code establishes a threshold for the labelling of added sulphites at 10mg/kg. VITAL® 2.0 does not make recommendations in relation to the labelling of sulphites from naturally occurring sources.
A. Population thresholds calculated for some allergenic foods/ingredients	Food Standards Agency	General comments • I am not convinced the Draft Opinion has addressed the points raised by Ireland as fully as it can be. I am disappointed that they were of a view that thresholds could not be determined yet they are being used in an unofficial and voluntary basis across sectors of the food industry. • The presentation of the text was a little clunky and would benefit with some formatting to make clear when moving from one section / topic to another. • The flow of the text makes it quiet cumbersome to read, this is particularly the case for the first 57 pages. • Due to the timing of the Irish mandate, the revised Opinion has not be able to include key data from EuroPrevall which omits vital data that may be of interest with regard to the development of allergen thresholds to inform precautionary

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		labelling • It was not clear from the document what search terms or inclusion criteria were used, furthermore it was unclear what the cut-off date was for papers to be considered. The UK are aware of several key papers which have used data from or associated with EU FP project EuroPrevall which have been published, are near to publication. It would be sensible to have these included and considered for the purpose of progress the allergen thresholds area. I believe that there are sufficient data for the large majority if not all of the Regulatory allergens at the level of protection stated in the Draft Opinion. • The section reviewing the methods was rather muddled it was not clear in which context these methods would be used; for example whether they were for routine diagnostics for food testing, experimental testing or clinical diagnostics. • Were there any data on performance criteria for methods to address the variety of methods and target analytes used? – I would consider this as a useful tool which would make results more comparable and to easier to link back to action thresholds or action levels for allergens. • Reference materials - whilst there are ones for milk and egg they are not similar to milk and egg ingredients used in foods due to the treatment they have undergone to preserve them. • There was no direct reference to VITAL 2 (used in Australia and NZ) and current thresholds used in other countries (such as Japan). I think these are important for consideration when reviewing processes in place in other countries and protecting public health. • Check whether all acronyms have been written in full before they have been used e.g. CAP, LTP , PEP-SCAN • The reference to DNA and PCR methods made no reference on their suitability where derivative ingredients were used i.e. egg white, egg yolk, egg lecithin, milk derivatives such as whey, casein. Are there issues with regard to amount of DNA available in the ingredient or confusion between the animal of origin (e.g. cow, sheep, goat) with the animal product e.g. milk • The review of minimal eliciting doses for all foods could benefit from better presentation to enable risk assessors to review this data easily. Suggest tabular format with type of foo d material, eliciting dose, type of food challenge etc.
A. Population thresholds calculated for some allergenic foods/ingredients	Food Standards Agency	Edits • Line 119 (page 4) and line 2516 (page 57) – I disagree, this assumed there is insufficient data for all 14 allergens, from the work performed a part of the VITAL2 review we know that the data group was sufficient for a number of allergens to be able to calculate reference doses and in turn action levels for precautionary allergen labelling • Line 576 (page 13) to consider inclusion of food intolerance as well as allergy. • Line 655 ….food-specific immunoglobulin class E (IgE) antibodies and / or other antibodies. "…or not" sounds like other factors (non-immunological) could be involved. • Table 1 – Respiratory tract – I note that 'stridor' is has not been included as one of the clinical features, I believe this is different from asthma.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 702 (page 17) suggest move sentence starting with "Angioedema is the presence of…" to the end of the paragraph. The section is covering urticarial and angioedema and the two conditions are intermingled in the text making it rather confusing to rea d. • Section 3.2.2. Vomiting- would this be considered to be more serious in adults than in children – are there data on this? • Line 799 (page 19) change 'celiac' to 'coeliac' • Line 839 (page 20) – change to "….within minutes after the ingestion of foods containing added sulphites" Need to make clear that legislation refers to added sulphites not naturally occurring sulphites. • Line 842 (page 20) typo 'airway' not 'airways' • Lines 884-889 (page 20) the text in this paragraph is rather clunky to read and does not lead into anything of significance especially with the line on exercise induced anaphylaxis which does not explain its presence or context within this particular section. • Section 5 (page 24-25) – management of food allergy – Recent clinical work on acquiring peanut tolerance through oral exposure is not covered here. • Section 7.1.2 (page 32) is not an environmental factor and repeats text later in the Opinion (page 41 Section 10) – suggest delete. • Section 8.3.2 (pag e 36) no mention of beta-lactoglobulin (BLG) though is covered in milk section. • Line 1832 (page 42) neoallergens – are these new allergens caused by aggregation or cleaving of the protein structure or the exposure of epitopes as the protein unfolded due to thermal processing. • Line 10.2 (Page 43) Enzymatic hydrolysis. Were there any papers on acid hydrolysis? For example wheat protein isolates being made through enzymatic as well as acid hydrolysis both have different effects on individuals. • Section 10.4 (Page 43) it would be useful to explain what HPP is. • Lines 1912-16 (page 44) would these be better placed under section 10.6 multiple treatments? • Line 2316 9page 53) define "high temperature" for cleaving DNA. i.e. would DNA be suitable for testing canned methods where a high temperature is required to remove C.botulinum.

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		• Line 3971 (page 91) – "Almonds are not nuts…" a little abrupt for the start of this sentence. Need to example which it is different. i.e. is a drupe not a nut. • Table 10 (page 92) need to explain the figures better, i.e. prevalence within general population and prevalence within the nut allergic population • Line 4551 (page 105) typo 'DBPCFC' not 'DBPCFG' • Section 18.4 (page 109) – any data on cross reactivity with fenugreek in peanut allergic individuals? • Line 5713 (page 132) remove the extra "Bernhisel-Broadbent" from the text. • Section 27 (page 173) it would be useful to include food which naturally contain sulphites as well as those who produce sulphites due to fermentation.
A. Population thresholds calculated for some allergenic foods/ingredients	The Allergen Bureau Ltd	Appendix A The Appendix reports ED estimates and other thresholds for a range of allergenic foods from a number of papers that have used all or part of the same clinical challenge data set ((Blom et al., 2013, Allen et al., 2014, Remington, 2013 & Taylor et al., 2014). Taylor et al 2014 reports the actual ED values determined by the Allergen Bureau VSEP, whereas Allen et al 2014 reports the recommendations, made by the VSEP to the Allergen Bureau, based from these ED values, for use as Action Levels in VITAL® 2.0. Both sets of data are shown in the table in the appendix without cross-reference to indicate that they report different aspects of common analysis. Klein Entink et al 2014 (Food and Chemical Toxicology 70 (2014) 134–143) have reported the determination of ED values from random subsets from the same databased used by the VSEP and have demonstrate the impact of sample size and dose interval range on the accuracy of the results obtained. Comparison between ED values obtained by different analys es requires reporting of sample sizes, distribution(s) used and dose interval ranges.
A. Population thresholds calculated for some allergenic foods/ingredients	TNO - Nederlandse Organisatie voor Toegepast Natuurwetenschappelijk Onderzoek	Page 265-268 Appendix A reports the population thresholds calculated for some allergenic foods/ingredients as is found in literature. However it should be mentioned that the populations mentioned in this table are, for a large part, the same population reported in different forms for different audiences. The reference of Remington 2013 is the dissertation which is underlying the science for the Taylor et al 2014 and Allen et al 2014 publications using the same dataset, but showing the EDs for different statistical models that are fitting the dataset. Though all three models show good fit, one is selected to report the EDs as in the official publication by Taylor et al 2014, which is also explained in the M&M section of the publication. For the derivation of the reference dose for precautionary labeling purposes as is described in the Allen et al 2014 paper. In addition, the EDs mentioned in the publication of Blom et al are a specific subset of the total population in Taylor et al

CHAPTER TEXT	ORGANISATION	COMMENT TEXT
		2014 (and Remington 2013 and Allen et al 2014). Additional comments regarding Appendix A: - The table in confusing and nearly impossible to read. - Why is peanut formatted differently than the rest of the allergens. - With multiple blank lines, the reference labelling column makes it impossible to distinguish which reference the table is referring to without going and studying the Taylor et al 2014 and Remington 2013 references. - Allen et al 2014 reports reference doses, not ED values. The reference dose is based on ED values but varies slightly in that expert judgment was used to derive the exact values by a combination of statistical models. - The Allen et al 2014 reference doses should not be reported as equivalent to the ED01. However, if the Scientific Opinion does report the reference doses in Appendix A, why does it not report the reference doses for soy, wheat, mustard, lupin, sesame, and shrimp which are based on the lower 95% CI of the ED05. - Appendix A footnotes o 1 – OK o 2 – OK o 3 – OK o 4 – If these a re 95% CI then why are they reported as ED05s and not in parentheses like the 95% CI are indicated in the table? o 5 – OK o 6 – OK o Combination of 5&6 – NOT possible, this combination is used throughout the table and is not possible from the reported values. Should be relabeled as 4&6 o 7 – The description of type of study is unclear as this footnote is not used in the table.
A. Population thresholds calculated for some allergenic foods/ingredients	VITAL Scientific Expert Panel (VSEP)	Appendix A The Appendix reports ED estimates and other thresholds for a range of allergenic foods from a number of papers that have used all or part of the same clinical challenge data set ((Blom et al., 2013, Allen et al., 2014, Remington, 2013 & Taylor et al., 2014). Taylor et al 2014 reports the individual ED values from the different statistical models determined by the Allergen Bureau VSEP, whereas Allen et al 2014 reports the consolidated recommendations, based from the ED values from multiple statistical models (cumulative discrete log-normal log-logistic Weibull) and expert judgment, which were made by the VSEP to the Allergen Bureau, for use as reference doses in VITAL® 2.0. Both sets of data are shown in the table in the appendix without cross-reference to indicate that they report different aspects of a common analysis. Klein Entink et al 2014 (Food and Chemical Toxicology 70 (2014) 134–143) have reported the determination of ED values from random subsets from the same databased used by the VSEP and have demonstrate the impact of sample size and dose interval range on the accuracy of the results obtained. Effective comparisons between ED values obtained by different analyses requires reporting of sample sizes, distribution(s) used and dose interval ranges.

GLOSSARY AND ABBREVIATIONS

BAT	basophil activation test
CMA	cow's milk allergy
Coeliac disease	Autoimmune adverse reaction to food triggered by the ingestion of gluten and related to prolamins found in wheat, barley and rye
CRD	component-resolved diagnosis
CRMs	certified reference materials
DBPCFC	double-blind placebo-controlled food challenge
DNA	deoxyribonucleic acid
ED*p*	population-based eliciting dose
ELISA	enzyme-linked immunosorbent assay
FAPAS	Food Analysis Proficiency Assessment Scheme
FLG-LOF	filaggrin loss-of-function
Food allergy	Adverse health effect arising from a specific immune-mediated response that occurs reproducibly on oral exposure to a given food, which can be mediated by food-specific IgE antibodies or not
Food intolerance	Non-immune-mediated adverse reactions to food
HHP	high hydrostatic pressure
HPLC-FLD	high-performance liquid chromatography-fluorescence detector
IgE	immunoglobulin E
LFD	lateral flow device
LOD	limit of detection
MED	minimum eliciting dose
MOED	minimum observed eliciting dose
MS	mass spectrometry
nsLTP	non-specific lipid transfer proteins
PDB-files	Protein Databank files
RP-HPLC-FLD	reversed-phase high-performance liquid chromatography-fluorescence detector
SBPCFC	single-blind placebo-controlled food challenge

Sensitisation	Positive SPTs or specific IgE to the offending food
SPT	skin prick test
WHO	World Health Organization