

GC response to an EFSA DRAFT SCIENTIFIC OPINION on the evaluation of allergenic foods and food ingredients for labelling purposes, by the EFSA Panel on Dietetic Products, Nutrition and Allergies (NDA)

The EFSA website allows a response text of maximum 3800 characters for each section of the draft opinion.

By way of introduction the document **ABSTRACT is as follows**

Following a request from the Food Safety Authority of Ireland, 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. In view of the request, the NDA Panel decided to update its previous opinions relative to food ingredients or substances with known allergenic potential listed in Annex IIIa of 2003/89/EC, as amended. These include cereals containing gluten, milk and dairy products, eggs, nuts, peanuts, soy, fish, crustaceans, molluscs, celery, lupin, sesame, mustard and sulphites. The Opinion relates to IgE- and non IgE-mediated food allergy, to coeliac disease, and to adverse reactions to sulphites in food, and does not address non-immune mediated adverse reactions to food. 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.

Comments on 1. INTRODUCTION

The Food Safety Authority of Ireland requested 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

This was a timely and relevant request and the EFSA NDA Panel are to be commended on their extensive work on this draft opinion.

The Panel note the EuroPrevall, study launched in June 2005, designed to estimate the prevalence of food allergy and exposure to known or suspected risk factors for food allergy across Europe in adults and children. However, the Panel note that prevalence data from that project have not been published and are not available to EFSA. This is disappointing and we urge EFSA to make every effort to access the EuroPrevall data and that the opinion should not be finalised until the Panel have had the benefit of the EuroPrevall data.

Comments on 2. Classification of adverse reactions to foods and definition of terms

The Panel have produced an excellent overview of the terms and conditions in this topic area. We note the Panel do not use the term 'food hypersensitivity' as the Panel consider that it is

ambiguous but remark that it is a useful term to describe the spectrum of conditions that include food allergy, celiac conditions and food intolerance.

Comments on 3. Clinical symptoms of food allergy

We welcome the widely drawn scope of this section, including as it does, multiple organ systems, (skin, GI Tract, respiratory system, eyes) and conditions (urticaria and angioedema atopic dermatitis, oral allergy syndrome, vomiting and gastro-oesophageal reflux disease, diarrhoea and enteropathies, infantile colic, constipation, asthma, laryngeal oedema, rhinitis and anaphylaxis). We concur with the conclusions that immune-mediated adverse reactions to foods manifest with clinical signs and symptoms of variable severity and duration, which may affect different organs and systems up to anaphylactic reactions and may occur at any age and that non IgE-mediated food allergy includes a wide range of diseases.

Comments on 4. Diagnosis of food allergy

The comprehensive nature of this section is commended and we particularly welcome the statement that measurements of IgG and IgG subclass antibodies against food antigens in serum have no role in the routine diagnosis of food allergy and should not be the basis for exclusion of particular foods from the diet. We concur that the principle diagnostic tools are a careful family and clinical history confirmed by exclusion of the suspected food and the subsequent amelioration of symptoms, and by the recurrence of symptoms on re-introduction of the offending food, ideally in double-blind placebo-controlled food challenges, provided that the initial symptoms were not life threatening.

We support the Panel in the need for standardisation of allergenic foods and preparations for diagnostic use, including oral challenge studies, and of derived allergens for Skin Prick testing, SPT, as well as for standard testing protocols in order to facilitate epidemiological and other multicentre studies on allergic reactions to foods.

The Panel notes that the radioallergosorbent test (RAST) is being increasingly replaced by quantitative immunochemical tests for the determination of food-specific serum IgE antibodies, sIgE. We consider the Panel should strengthen this point as RAST has been superseded by sIgE.

Comments on 5. Management of food allergy

The Panel concludes dietary avoidance of specific allergenic foods in combination with nutritional advice is the mainstay of management in IgE- and non IgE-mediated food allergy. Close monitoring of growth of infants and children with food allergy is advised, as well as re-evaluation of food allergy at regular intervals to avoid unnecessary dietary restrictions.

This section is a useful summary of standard immunotherapies. We urge the Panel to update the section with more recent work on oral immunotherapy, e.g. "Assessing the efficacy of oral immunotherapy for the desensitisation of peanut allergy in children (STOP II): a phase 2 randomised controlled trial, Katherine Anagnostou, Sabita Islam, Yvonne King, Loraine Foley, Laura Pasea, Simon Bond, Chris Palmer, John Deighton, Pamela Ewan, Andrew Clark, Lancet January 30th 2014.

Comments on 6. Epidemiology of food allergy

The Panel takes a necessarily conservative view of the studies reviewed in this section noting that the prevalence of food allergy in Europe is uncertain. Using food challenges as a criterion for

diagnosis, the prevalence of food allergy in Europe has been estimated to be between 3 and 4 %, both in children and adults. The Panel further notes there are insufficient objective data to conclude on time trends with respect to the prevalence of food allergy in Europe. About 75 % of allergic reactions among children are due to egg, peanut, cows 'milk, fish and various nuts. About 50 % of allergic reactions among adults are due to fruits of the latex group and of the *Rosaceae* family, vegetables of the *Apiaceae* family, and various nuts and peanuts. Anaphylactic reactions have been reported to foods not included in EU labelling law.

The European Academy of Allergy & Clinical Immunology (EAACI) has reviewed prevalence (Nwaru *et al.*, on behalf of the EAACI Food Allergy & Anaphylaxis Guidelines group, Prevalence of common food allergies in Europe: a systematic review and meta-analysis, *Allergy* 2014, DOI:10.1111/all12423) also observed significant heterogeneity between studies and called for standardisation of the methods of assessment of food allergies and strategies to increase study participation.

No doubt the Panel will wish to include the EAACI review and meta-analysis in the next iteration of its opinion.

Comments on 7. Influence of environmental and individual factors in the distribution of food allergies

The Panel concludes the occurrence of food allergies requires susceptibility of the host and exposure to the allergen. Geographical variation in the prevalence of food allergy is due to differences in genetic regional and local factors, like pollen exposure or differences in food habits. Extrapolations of prevalence data on specific food allergies from a single European country to the entire European population are of limited accuracy due to differences in exposure to the offending foods and eating habits.

No doubt the Panel will wish to include the conclusions of the EAACI Food Allergy & Anaphylaxis Guidelines in the next iteration of its opinion.

Comments on 8. Characterisation of food allergens

This section of the consultation is a comprehensive review of proteomic, spectroscopic and gene cloning approaches to the characterisation of allergen proteins. Allergen proteins have been classified into families on the basis of their sequence and three dimensional structures. However, although common structural features of proteins and their biological activity have been tentatively related to their antigenicity, it is not possible to predict the allergenicity of a protein on the basis of these two parameters only. Immunological and clinical data are required to classify a protein as a food allergen. We have nothing to add to this section of the Consultation.

Comments on 9. Cross-reactivities

The Panel concludes cross-reactivity occurs when IgE antibodies originally triggered against one antigen also bind a different antigen. Not all cross-reactivities identified *in vitro* are of clinical significance, and although most clinical cross-reactions are mediated by IgE antibodies, T cells may also be involved. However, *in vitro* cross-reactivity testing can help understanding allergenicity to multiple foods, as well as improving diagnosis and management of food allergy. We have nothing to add to this section of the Consultation.

Comments on 10. Effects of food processing on allergenicity

The Panel has given an excellent overview of the influence of food processing on protein allergenicity and concludes the allergenic activity of a complex food may decrease, remain unchanged, or even increase by food processing. Considering the multiplicity of the allergenic structures contained in a whole food and that different proteins may be differently affected by the same treatment, the impact of food processing on the structural and allergenic properties of

allergenic foods/ingredients is difficult to predict. In addition, the extent to which allergenic proteins are modified during food processing depends on the type of process and its conditions, the structure of the proteins, and the composition of the matrix. Although the effects of different (technological and cooking) treatments on the IgE-binding capacity of several allergens have been investigated, less information is available on the effects of processing on clinical reactivity. We concur with these conclusions and add that these factors also impact on the analytical chemistry of allergen proteins.

Comments on 11. Methods for the detection of allergens and allergenic ingredients in food

The Panel have produced a comprehensive review of analytical strategies for allergenic proteins which resonated with our own experiences. Reliable methods for the detection and quantification of food allergens are necessary to ensure compliance with food labelling legislation. These methods need a well-defined reference material (certified reference materials – CRMs – for quantitation) and a reliable method of recovery. Reference materials developed by different producers are commercially available for most major food allergens, but the results obtained may not be comparable. To the Panel's knowledge, only a peanut test material has been produced by the Institute for Reference Materials and Measurements (IRMM) IRMM-481, containing five different varieties of peanuts. For egg detection, egg powder from the National Institute of Standards and Technology (NIST) (NIST RM-8445) and for milk the NIST fat-free milk powder (NIST RM-1549), are available though not certified.

We add the following comments. The IRMM materials do not represent incurred reference materials at analytically relevant concentrations.

Flawed allergen analysis hinders detection and measurement of allergens, which is also important for food labelling¹, defining threshold levels and detecting food fraud. ELISA, the workhorse technique, exhibits variable and manufacturer-specific sensitivities and cross-reactivity.² Structural changes by food processing or sample extraction may prevent detection by ELISA or LC-MSⁿ. PCR identifies the source species not the allergen protein, LC-MSⁿ methods could be used for multiplex high throughput analysis, definitive confirmation of epitope, protein molecular identity and measurement traceability. Metrological traceability to the SI³, enabling valid comparison between measurements carried out in different laboratories has been largely neglected. Metrological traceability of allergen proteins is currently possible only by MS based absolute quantification.⁴ To our knowledge SI traceable assignment of the concentration of allergenic proteins in food has had very limited study^{5,6} and would greatly facilitate the standardisation of analytical techniques for allergens.

What needs to be done?

Improve the robustness and accuracy of allergen analysis by ELISA, PCR and LC-MSⁿ, by investigating:

- the interrelation between these techniques for protein allergens and the bias associated with each;

¹ Food Information to Consumers, Regulation 1169/2011

² Marianne Defernez, *et al*, 2013, Management of food allergens: from threshold doses to analysis in foods, Food Standards Agency Project T07062, [Final Report](#)

³ Bureau International des Poids et Mesures, BIPM, The International System of Units (SI), 8th edition 2006

⁴ Barwick, V., & Wood, S, *J. Anal. At. Spectrom.*, 25, 785–799

⁵ A Cryar, *et al*, 2012, *J. Assoc. Public Analysts* (Online), 40: 77-80 – open access http://www.apajournal.org.uk/2012_0077-0080.pdf

⁶ A Cryar *et al*, 2013, *J AOAC Int.*, 96, 1350-1361

- novel means of overcoming issues such as poor recovery of allergen proteins from food matrices and effects of food processing on measurement variability;
- limits of detection and objective comparisons of sensitivity, and expressions of units (copy numbers for PCR and mg/kg for ELISA and LC-MSⁿ) between techniques;
- building on published work^{10,11} on absolute quantification and metrological traceability of allergen proteins;
- the application of absolute quantification of allergen proteins to proficiency testing;
- the development of allergen reference materials and their certification; and
- Promoting global cooperation between centres of excellence in allergen protein measurement and metrological traceability to address the above problems.

We also ask the Panel to note that as a first step to produce a reference material with a realistic and challenging food matrix and potential clinical relevance, we have put on the market a prototype quality control set, (blank material and a material with peanut protein added at 10 mg/kg), based on the EuroPrevall study [chocolate dessert](#) matrix which was used for low-dose threshold studies in food allergic individuals.

Finally we would ask the Panel to note our own review:

Food Allergen Detection: A Literature Review 2004 – 2007, M J Walker, P Colwell, S Elahi, K Gray and I Lumley. *J. Assoc. Public Analysts* (Online), 2008, 36, 1-18

Other references are given as footnotes in the text.

Comments on 12. Determination of thresholds for allergenic foods/ingredients

The Panel note 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. The Panel Opinion is considers specific allergenic foods/ingredients, minimal (observed) eliciting doses for individuals reported in challenge studies, rather than estimated thresholds for populations. We agree this is a difficult area however we urge the Panel to consider Muraro *et al.* 2014, Protecting Consumers with Food Allergies, EAACI Guidelines, in EAACI Food Allergy and Anaphylaxis Guidelines, and references therein. This publication establishes a draft set of suggested reference doses for 12 major allergens.

We suggest further that the Panel should consider co-opting a subgroup of the EAACI Food Allergy & Anaphylaxis Guidelines group into the Panel to assist especially with horizon scanning of studies underway with a bearing on the opinion so that the panel may time the finalisation of the opinion with the benefit of key studies currently under way and recently published.