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A protocol for a systematic review to identify allergenic tree nuts and the molecules responsible for their allergenic properties

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ABSTRACT

Food regulations require that tree nuts and derived ingredients are included on food labels in order to help individuals with IgE-mediated allergies to avoid them. However, there is no consensus regarding which tree nut species should be included in this definition and specified on food labels. Allergen detection methods used for monitoring foods target allergen molecules, but it not clear which are the most relevant molecules to choose. A modified population-exposure-comparators-outcome (PECO) approach has been developed to systematically review the evidence regarding (1) which allergenic tree nuts should be included in food allergen labelling lists and (2) which are the clinically relevant allergens which should be used as analytical targets. A search strategy and criteria against which the evidence will be evaluated have been developed. The resulting evidence will be used to rank tree nuts with regards their ability to cause IgE-mediated allergies, and allergen molecules regarding their capacity to elicit an allergic reaction. The results of the systematic review will enable risk assessors and managers to identify tree nut species that should be included in food allergen labelling lists and ensure analytical methods for determination of allergens in foods are targeting appropriate molecules.

1. Background

IgE-mediated food allergy affects approximately 1.5% of adults and 5–6% of children in Europe although most infants and young children "outgrow" their food allergy by school age (Nwaru et al., 2014) with tree nuts being estimated to cause around 0–1.9% of food allergies (McWilliam et al., 2015). The prevalence of food allergy varies around the world, and whilst sensitisation to a wide variety of foods is high in countries like India, the prevalence of probable food allergy is low (Mahesh et al., 2016). Differences in methodology may in part be responsible for these variations although genetic and environmental factors also contribute (Rona et al., 2007; Nwaru et al., 2014; McWilliam et al., 2015). Whilst more than 170 different foods have been reported to cause IgE-mediated allergic reactions (Hefle et al., 1996), the majority of allergies are caused by a relatively small number of foods including egg, milk, fish, shellfish, peanut and tree nuts (Nwaru et al., 2014; McWilliam et al., 2015; Venter et al., 2016). Since there is currently no accepted therapy for food allergy, individuals diagnosed with the condition must practise food avoidance, often lifelong. Those individuals thought to be at risk of having a severe reaction are also given rescue medication such as anti-histamines and self-injectable adrenaline, should they accidentally consume some of their problem food.

In order to help allergic consumers avoid their problem food, a list of priority allergenic foods have to be labeled at whatever level they are included in a recipe, based on the foods listed in the Codex Alimentarius Commission labeling recommendations (CodexAlimentariusCommission, 1999). The Codex list includes

Abbreviations: CASP, Critical appraisal Skill Program; DBPCFC, double blind placebo controlled food challenges; EAACI, European Academy of Allergy and Clinical Immunology; EFSA, European Food Safety Authority; ELISA, enzyme-linked immunosorbent assay; PECO, Population, exposure, comparator and outcome; PAL, Precautionary allergen labelling.

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"tree nuts", although the specific plant species covered by this phrase are not always defined in regulations implemented across the world. In general expert opinion has been used to inform decisions as to which foods should be included in food allergen labeling lists, although systematic approaches have been proposed to identify allergenic foods of public health importance that must be actively managed (Bjorksten et al., 2008; Houben et al., 2016b; van Bilsen et al., 2011). In addition to mandatory labeling of allergenic ingredients, precautionary allergen labelling (PAL) may also be used to warn the allergic individual about the unintended presence of allergens through the use of phrases, such as "may contain" (DunnGalvin et al., 2015). Effective analytical methodology is required to help support risk assessment and management of allergenic ingredients using approaches such as those developed by the Voluntary Incidental Trace Allergen Labelling (VITAL) expert group (Taylor et al., 2014). Analysis of allergens is used for both in validating cleaning protocols in factories as well as monitoring ingredients and finished foods for unintended allergens. However, there are many limitations with current analytical methods for allergens (Walker et al., 2016) and it is not always clear which allergen molecules represent the hazard for allergic consumers and should be used as analytical targets for new methods, such as protein mass spectrometry.

We propose to undertake a systematic review of the literature to assess the strength of evidence supporting the inclusion of particular tree nut species in priority lists of allergenic foods, and to help identify clinically relevant allergenic molecules in those foods to be used as analytical targets in allergen analysis. (McWilliam et al., 2015; Venter et al., 2016). The application of systematic reviewing to food hazards, such as allergens, is relatively novel, and it is recognised that there is a need to adapt protocols used in medicine to the needs of evidence-based toxicology (Stephens et al., 2016). We have developed a protocol for the systematic review built on an approach previously described for identifying allergenic foods of public health importance (Bjorksten et al., 2008; Houben et al., 2016a; van Bilsen et al., 2011). It is based on guidance provided by the European Food Safety Authority (EFSA, 2010) which draws on approaches developed in the health care field (Higgins and Green, 2011; CRD, 2009) and applies PRISMA guidelines (Moher et al., 2009).

2. Study design

The primary question being addressed is "What is the evidence that the clinical manifestation of an IgE-mediated allergic reaction is caused by ingestion of a particular tree nut species?"

The secondary question being addressed is "Which tree nut molecules are recognised by serum-IgE from tree nut allergic individuals and are responsible for causing an IgE-mediated adverse reaction to those foods?"

The primary question will be addressed using a PO approach (EFSA, 2010) the population (P) being the patient population evaluated for an IgE-mediated allergy to food and the outcome (O; or condition of interest) being whether they suffer from IgE-mediated allergy to tree nuts (Fig. 1). The population can include patients drawn from either prospective cohort studies, longitudinal cohorts, or cross-sectional studies and case series. The outcome is then graded with regards the quality of diagnosis (test accuracy), based on the principals laid out in the EAACI Food Allergy Guidelines (Muraro et al., 2014; Soares-Weiser et al., 2014) and criteria proposed by Bjorksten and co-workers (Bjorksten et al., 2008). This will allow the quality of studies and the evidence that documented adverse reactions are caused by an IgE-mediated mechanism to be assessed and provide some indication of the severity of reactions.

The secondary question will be addressed using a modified population, exposure, comparator and outcome (PECO) (EFSA, 2010) approach (Table 1; Fig. 1). In the modified approach the population is the one identified in addressing the primary question that has been classified as having either probable or confirmed food allergy. The exposure (E) element of PECO is taken as the exposure to tree nut allergens as indicated by the detection of tree-nut specific serum IgE and/or positive skin prick testing with tree nuts, tree-nut extracts or purified tree nut allergens. The test accuracy will be assessed in terms of the quality of the IgE binding studies performed together with the quality of the allergen extracts and purified allergens used. The comparison (C) is then made with regards the prevalence of sensitisation to the different allergen molecules in the population (P). The allergens will also be compared with regards their potency as indicated by their ability to bind IgE or trigger mediator release in an effector cell assay, such as the stripped-basophil histamine release assay. The outcome [O] relates to the evidence indicating that a particular allergen molecule is responsible for eliciting IgE-mediated allergic reactions in the population. If data are of sufficient quality, some indication of their potency may also be assessed through a meta-analysis of outcomes, such as skin prick test wheal diameter or levels of allergen specific IgE.

3. Search strategy

Initially a list of tree nuts included in allergen labelling legislation in Europe, USA and other jurisdictions was compiled (Supplementary file 1). Currently 31 countries and one jurisdiction in the world have implemented food allergen labelling regulations, and three countries have proposed a food allergen legislation draft for consideration. Several have listed specific tree nut species and these were used as the basis to defining the search terms (Table 2). These search terms will be applied with validated study designed filters for retrieving any other relevant systematic reviews (Wilczynski and Haynes, 2007) and sound diagnostic studies (Wilczynski and Haynes, 2005) and used to search MEDLINE (OVID), ISI Web of Science, and Scopus (Falagas et al., 2008) from inception to 30-August-2017. Additional references will be located through searching the allergenic food database InformAll, a searchable technical database for food allergy (plant and animal allergenic foods), hosted by the University of Manchester and based on peer reviewed articles which have been reviewed by a panel of expert referees (InformAll). This will be complemented by searching the references cited in the papers identified in the search, technical reports and other literature that has not been peer reviewed but is publicly available. The database will be searched without language restrictions. If the abstract of a non-English article is identified as being relevant, where possible, it will be translated into English. The research process will be fully documented to allow the search to be assessed and reproduced.

4. Study selection

Articles identified in the searches will be evaluated against inclusion and exclusion criteria defined in Table 3. All references will be uploaded into EndNote and duplicate copies of the same article be removed using a combination of automatic (using software such as Distiller) and manual screening. Study titles and abstracts will be independently reviewed by two team members (BJ, ENCM) using the selection criteria described above and categorised as included, excluded, and unsure. The full text of research studies in the unsure category will be retrieved and re-categorised as included or excluded. Discrepancies will be resolved by discussion with the whole team (BJ, ENCM, AS, PP and MS).