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## **Supporting document 1 Proposal P1044 – Plain English Allergen Labelling**

**Safety Risk assessment**

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### **Executive summary**

FSANZ is preparing a proposal to consider potential changes to the Australia New Zealand Food Standards Code (the Code) that introduce requirements to use plain English allergen labelling (PEAL). As part of this proposal, consideration has been given to the clinical significance of mollusc allergy in Australia and New Zealand, which tree nuts are important in food allergy, and whether all cereals that contain gluten are also of concern for food allergy.

Three mollusc classes (bivalves, gastropods and cephalopods) have been implicated in cases of food allergy. Although there are few published data specifically regarding the prevalence of mollusc allergy in Australia and New Zealand, FSANZ's Food Allergy and Intolerance Scientific Advisory Group (FAISAG) has advised FSANZ that mollusc allergy is of clinical significance in the two countries.

There is some evidence of cross-reactivity or co-sensitisation between molluscs and crustaceans based on serological testing, self-reporting and clinically diagnosed allergy. However based on available data the extent of clinically relevant cross-reactivity is likely to be relatively low.

FAISAG previously advised FSANZ that nine tree nuts are important allergens: almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. Clinically defined food allergy, clinical cases or positive responses to oral food challenges in Australia and/or New Zealand have been reported for all of these tree nuts. Clinical responses to more than one tree nut have also been reported to occur in up to a third of allergic individuals, and the incidence of reactions to multiple nuts may be even higher based on the advice of FAISAG.

There is little evidence relating to the allergenicity of less commonly consumed tree nuts, and FAISAG considered that the available information did not indicate a need to amend its previous advice on significant tree nut allergens. However these nuts are currently unlikely to be widely used in processed foods and may only be consumed by small numbers of individuals. Therefore this conclusion may need to be revised if use patterns change significantly.

Food allergy to barley, rye and oats is IgE-mediated and distinct from gluten intolerance. Several studies have reported positive allergic responses to food challenges with barley, rye and/or oats in children or adults, and in most of these studies individuals were confirmed as not having coexisting coeliac disease. Gluten and non-gluten proteins have been identified as allergens in barley.

There is little data on the prevalence of allergy to these cereals in Australia and New Zealand. The FAISAG advised FSANZ that they do see cases of rye and barley allergy, but these are not common. Oat allergy is very rare and problems are usually due to cross-contamination with other cereals.

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# 1 Introduction

FSANZ is developing a proposal to consider potential changes to the Australia New Zealand Food Standards Code (the Code) that introduce requirements to use plain English allergen labelling (PEAL).

This proposal stems from previous work by FSANZ which identified that allergen declarations on foods may not always be easily recognised or understood by consumers with food allergy. A 2015-2016 review ([W1070](#)) identified that the terminology used to declare allergens is a primary cause of this problem. The way in which allergens are declared on labels may sometimes be too vague (e.g. 'gluten containing cereals' rather than 'rye'), not accurate (e.g. 'fish' for foods containing molluscs), or too technical (e.g. 'sodium caseinate' without an indication that it is from a dairy source).

The W1070 Review concluded that there is a lack of standard practices for declaring allergens, as well as a lack of clarity in the Code on how terminology should be used to declare allergens.

Prior to the W1070 Review, FSANZ completed a review of the regulatory management of food allergens (W3 Review; FSANZ 2010). Scientific and clinical research on three key issues relating to food labelling requirements was reviewed as part of this work. These issues were: the allergenicity and cross-reactivity of finfish, crustaceans and molluscs; identifying tree nuts of clinical significance in the context of food allergy; and the distinction between wheat allergy and gluten-related adverse reactions.

In developing the PEAL proposal a number of additional technical questions relating to mollusc, tree nut and cereal allergies have been identified. This supporting document (SD) sets out responses to those questions, based on reviews of the relevant scientific and clinical literature and consultation with FSANZ's Food Allergy and Intolerance Scientific Advisory Group (FAISAG).

FAISAG provides expert advice to FSANZ on a range of matters related to food allergy and intolerance to help assess and manage risk to allergic consumers. Information on the membership of the FAISAG is available at: <http://www.foodstandards.gov.au/science/expertise/Pages/Food-Allergy-and-Intolerance-Scientific-Advisory-Group.aspx>.

## 2 Mollusc allergy

### 2.1 Background

The definition of 'fish' in the Code is as follows: *'fish means a cold-blooded aquatic vertebrate or aquatic invertebrate including shellfish, but not including amphibians or reptiles'*. The term shellfish is not defined in the Code but according to the Maquarie Dictionary is comprised of molluscs and crustacea. As a result of this broad definition, FSANZ is aware that the term 'fish' could potentially be used by manufacturers to declare both finfish and shellfish. There is also an overlap between this broad definition and the separate requirement in the Code to declare crustacea as an allergen.

The W1070 Review found that currently there is some confusion amongst manufacturers as to how to declare the presence of molluscs and crustacea. While individual mollusc and crustacean ingredients are being declared in the ingredient list, some of the labels on these foods are also displaying a 'contains' summary statement that declares the presence of 'fish'.

It was therefore concluded that the Code needs to be clearer with respect to the terms 'fish'/'finfish', 'crustacea' and 'molluscs' for allergen declaration purposes.

FSANZ's 2010 review of the regulatory management of food allergens identified that molluscs are allergenically distinct from fish, but was equivocal on whether they are allergenically distinct from crustaceans. In addition, stakeholders raised differing views on what they consider to be molluscs during the W1070 Review.

Clarifying the crustacean/mollusc allergen profile will assist FSANZ to develop an appropriate labelling requirement for molluscs. The following risk assessment questions have therefore been considered:

- What is the prevalence of mollusc allergy in Australia and New Zealand?
- What taxonomical classes of molluscs are specifically implicated in food allergy?
- What is the extent of cross-reactivity between crustacean and mollusc allergies?

## **2.2 Responses to risk assessment questions**

### **2.2.1 What is the prevalence of mollusc allergy in Australia and New Zealand?**

Seafood allergy is considered to be common in Western countries such as Europe, the USA and Australia (Lopata et al 2016).

Seafood was recently reported to be the most common trigger of food-related anaphylaxis fatalities in an Australian study, accounting for 50% of food-related fatalities recorded in the National Coronial Information System (NCIS) between 2000 and 2013 (Mullins et al 2016). This figure is not necessarily representative of the proportion of food-related allergies nationally overall, as coroners' inquests following fatal anaphylaxis are not currently mandated in Australia. Therefore the NCIS potentially only contains a subset of all cases.

Seafood has also recently been reported as the most common food associated with adult hospital presentations of food-induced anaphylaxis in a New Zealand study (Kool et al 2016). Seafood was linked to 31% of cases for which the food type was reported, although the food type was only reported for 21% of all cases.

In another Australian study, 4% of food-related cases of anaphylaxis in children presenting to the Royal Children's Hospital in Melbourne were associated with seafood consumption (de Silva et al 2008). In a study of 457 adults in Melbourne, Australia, 9.7% reported nearly always having illness after eating seafood, and 3.3% reported illness following consumption of shrimp (Woods et al 2002).

Most recently, Sasaki et al (2017) reported the prevalence of food allergy in a cohort of 10-14 year olds in Melbourne. The prevalence of clinic-defined shellfish allergy was 0.3%, while the self-reported prevalence was 0.8%.

While these studies report anaphylaxis or other adverse effects associated with consumption of seafood, generally they do not identify the specific type involved (de Silva et al 2008; Hill et al 1997; Kool et al 2016). Only one study specifically reporting prevalence of mollusc allergy in Australia was identified, and no reports on its incidence in New Zealand were found. Among 167 children presenting at an allergy clinic in Sydney with a history of a definite clinical reaction to seafood (based on a convincing clinical history together with evidence of sensitisation and/or positive food challenge) between 2006 and 2009, nine children (5%) were allergic to molluscs (seven to squid, two to oyster) (Turner et al 2011).

Of the 11 cases of seafood-related anaphylaxis fatalities in the Australian NCIS database, one each was associated with prawn, lobster or fish, three with unspecified seafood and five with unspecified shellfish (Mullins et al 2016). Molluscs were not specifically identified.

FAISAG noted that there is little information in the public literature but considered that mollusc allergy is of clinical significance in Australia and New Zealand. Whilst mollusc allergy is relatively uncommon in children, cases of anaphylaxis following consumption of molluscs such as calamari have been seen. The advisory group also considered that mollusc allergy may be more of an issue for children of ethnic minority groups for whom mollusc consumption is higher than among Caucasian children. Significant late-onset mollusc allergy is also seen in adults.

## **Conclusion**

Seafood allergy is relatively common in Australia and New Zealand and is a major contributor to food-associated anaphylaxis. However, few data are available regarding the prevalence of allergy to specific types of seafood, including molluscs. One study of Australian seafood allergy patients reported that the incidence of mollusc allergy in this group was 5%. The opinion of the FAISAG was that although specific information on the prevalence of mollusc allergy is not available, mollusc allergy is of clinical significance in Australia and New Zealand.

### **2.2.2 What taxonomical classes of molluscs are specifically implicated in food allergy?**

Molluscs are classified into eight classes, of which three are important as food and therefore considered relevant in the context of food allergy. These are 1) gastropods such as abalone and land and marine snails, 2) bivalves such as oyster, mussel, scallop and clam, and 3) cephalopods such as squid and octopus.

Allergic reactions to all three classes have been reported. The major mollusc allergen tropomyosin has been identified in many mollusc species including bivalves such as clams, mussels, oysters, razor shells and scallops, gastropods such as abalones, whelks and snails, and cephalopods such as octopus and squid (reviewed by Faber et al 2017). A number of different types of mollusc have been reported to cause allergy including mussel (Lopata and Jeebhay 2001; Sicherer et al 2004; Vidal et al 2015), clam (Sicherer et al 2004; Vidal et al 2015), oyster (Lopata and Jeebhay 2001; Sicherer et al 2004; Turner et al 2011), squid (Carrillo et al 1992; Turner et al 2011), octopus (Osterballe et al 2009; Damiani et al 2010), limpet (Carrillo et al 1994) and abalone (Lopata and Jeebhay 2001).

Species belonging to the classes polyplacophora (chitons) and scaphopoda (tusk shells) are sometimes eaten (Wu and Williams 2004), however no reports of food allergy relating to consumption of these species have been identified. It is not clear if this is due to relatively low levels of consumption of these species or a lack of allergenicity.

## **Conclusion**

Molluscs of the classes bivalves, gastropods and cephalopods are important as food, and all have been implicated in cases of food allergy. While some other classes of mollusc are reportedly consumed in some countries, no reports of food allergy relating to these species have been identified. It is not clear if this is due to relatively low levels of consumption or a lack of allergenicity.

### **2.2.3 What is the extent of cross-reactivity between crustacean and mollusc allergies?**

Cross-reactivity relates to immunoglobulin E (IgE) antibodies originally triggered against one antigen also responding to another antigen. Cross-reactions can occur between proteins that have a high amino acid sequence homology and/or with a similar 3D structure or common epitopes (reviewed by EFSA 2014).

Co-sensitisation relates to the production of IgE antibodies against different proteins in two different foods in the same individual. Common measures of sensitisation such as skin prick tests or serum IgE antibodies are not able to distinguish between co-sensitisation and cross-reactivity (EFSA 2014). However other methods such as the use of inhibition assays may be more reliable predictors of cross-reactivity (Aalberse 2007).

A review of the available literature on the likely extent of cross-reactivity between crustacean and mollusc allergies is set out below. It considers:

- types of shellfish allergens
- studies based on skin prick tests or measures of serum IgE
- studies based on self-reporting
- studies based on challenge or other clinical diagnoses of allergy

## **Shellfish allergens**

Tropomyosin has been identified as the major allergen in many molluscan species (Ishikawa et al 1998; Leung et al. 1996; Miyazawa et al 1996), and is also a major allergen in crustaceans (reviewed by Lopata et al 2016).

Tropomyosin is generally considered to be important for cross-reactivity between molluscs and crustaceans, however sequence homology between mollusc and crustacean tropomyosin is relatively low compared to that between different mollusc species or between different crustacean species (Kamath et al 2013; Leung et al 1998; Moyomata et al 2006; Motoyama et al 2007; Lopata et al 2016). It has been suggested that this may explain the more limited cross-reactivity seen between crustaceans and molluscs compared to that within crustaceans or within classes of molluscs (EFSA 2014).

A number of other non-tropomyosin allergens have also been identified in molluscs and crustaceans. Other allergens identified in crustaceans include arginine kinase, myosin light chain, myosin heavy chain, sarcoplasmic calcium binding protein, troponin C and triose phosphate isomerase (reviewed by Lopata et al 2016 and Pedrosa et al 2014). Non-tropomyosin allergens identified in molluscs include arginine kinase, myosin heavy chain and paramyosin (Lopata et al 2016; Pedrosa et al 2014).

The role of non-tropomyosin allergens in cross-reactivity between crustaceans and molluscs is not well defined at present. To date, only tropomyosin allergens are listed as molluscan food allergens in the WHO/IUIS database, which is considered to be reflective of a relative lack of systematic studies on mollusc allergens (EFSA 2014).

### ***Evidence of cross-reactivity between crustaceans and molluscs***

#### *Studies based on skin prick tests or measures of serum IgE*

Sensitisation to both molluscs and crustaceans has been identified through serological and/or skin prick testing in a number of studies. The clinical relevance of these findings is unclear in some cases, although the individuals included in some studies had a history of symptoms following consumption of molluscs and/or crustaceans.

In some cases cross-reactivity or co-sensitisation appears to only be found between certain species, either within or between mollusc or crustacean shellfish groups (Carrillo et al 1992; Carrillo et al 1994). For example, among 48 patients with a history of shellfish hypersensitivity, a positive skin prick association was found between cephalopods and clams and between cephalopods and crustaceans, but not between crustaceans and clams (Castillo et al 1994). In another study, however, serum from nine patients with known anaphylaxis to shrimp reacted with a 38 kDa protein, identified as tropomyosin, in all 13 different crustaceans and molluscs tested (Leung et al 1996).

In general, studies of sensitisation have found that a proportion of individuals are sensitised to molluscs and crustaceans, some to molluscs only and some to crustaceans only (Laffond Yges 1996; Lopata and Jeebhay 2001; Turner et al 2011; Wu and Williams 2004). The relative proportions vary between studies.

#### *Studies specifically assessing cross-reactivity*

Several studies included tests intended to measure cross-reactivity, rather than co-sensitisation. Methods used include inhibition assays and assessment of antibodies specific to one allergen to see if they react with another allergen.

In reverse enzyme immunoassay (REIA) inhibition assays using pooled serum from seven patients with squid allergy, the response to cooked squid was partially inhibited by oyster, but not by octopus, mussels or round clams (Carrillo et al 1992).

Miyazawa et al (1996) demonstrated cross-reactivity between the major squid and shrimp allergens, Tod p 1 and Pen o 1 – both forms of tropomyosin – respectively. Pre-absorption of sera taken from shrimp allergic patients with recombinant shrimp tropomyosin resulted in complete inhibition of binding to tropomyosin in a range of molluscs including gastropods, bivalves and cephalopods (Leung et al 1996).

The crustaceans shrimp, crab, lobster and crayfish were all found to inhibit oyster radioallergosorbent test (RAST) responses, with the crustacean extracts being more potent inhibitors than oyster extracts (Lehrer and McCants 1987).

#### *Studies based on self-reporting*

Self-reports of shellfish allergy include individuals reporting responses to both molluscs and crustaceans, or to just one of these groups (Carrillo et al 1992; Carrillo et al 1994; Castillo et al 1994; Lehrer and McCants 1987; Ishikawa et al 1998; Ishikawa et al 1999; Wu and Williams 2004). These reports are summarised in Table 1.

**Table 1: Self-reports of allergy to molluscs and/or crustaceans**

Author	Study Group	Response to Crustaceans and/or Molluscs
Carrillo et al 1992	7 patients with symptoms suggestive of allergy after eating or inhaling vapour from cooked squid (a mollusc)	- 6/7 had symptoms after eating shrimp - None reported reactions to other molluscs (octopus, oyster, round clam and mussel) or to crustaceans (lobsters and crab)
Carrillo et al 1994	6 patients with anaphylactic symptoms due to limpet (a mollusc) ingestion	- All patients tolerated different molluscs and crustaceans after the anaphylactic reaction
Castillo et al 1994	48 patients with a history of shellfish hypersensitivity	- 44 patients showed symptoms after eating shellfish - Shrimp caused symptoms in 33 cases - Squid caused symptoms in 24 cases - Most frequent clinical association: shrimp-squid-lobster (18 patients) - History of cephalopod hypersensitivity associated with bivalve sensitivity - Cephalopod and bivalve hypersensitivity not associated with crustacean
Lehrer and McCants 1987	Patients with symptoms following ingestion of oysters and/or crustaceans	- 6 patients with symptoms on ingestion of oysters only - 7 patients with symptoms on ingestion of oysters and crustaceans - 12 patients with symptoms on ingestion of crustaceans, but either lack of hypersensitivity or lack of prior exposure to oysters
Ishikawa et al 1998	Participants intolerant to molluscs and/or crustaceans	- 3 participants intolerant to molluscs and crustaceans - 1 participant intolerant to crustaceans only
Ishikawa et al 1999	Participant with hypersensitivity to molluscs and crustaceans	- 1 participant with immediate hypersensitivity reactions after ingesting molluscs and crustaceans
Wu and Williams 2004	14 Patients with suspected shellfish allergy	- 1 reacted to crab and clam - 4 reacted to crab and shrimp (both crustaceans) - Others reacted to one mollusc or crustacean species only

*Studies based on challenge or other clinical diagnoses of allergy*

A limited number of studies report on individuals who have been diagnosed with allergy to both molluscs and crustaceans. However, these studies also include patients that have only been diagnosed with allergy to one or the other shellfish group. These studies are summarised in Table 2.

**Table 2: Reports of clinically-diagnosed mollusc and/or crustacean allergy**

Author	Study Group	Method of Diagnosis	Response to Molluscs and/or Crustaceans
Vidal et al 2015	31 patients with anaphylaxis following crustacean ingestion	Self-reports of presence/absence of similar symptoms after eating mollusc, or open food challenge	- 14/31 had mollusc allergy - 17/31 were mollusc tolerant
Crespo et al 1995	24 children with shellfish allergy	Positive clinical history, positive specific IgE by skin prick test and RAST, and open food challenge	- 10/24 had mollusc allergy - 23/24 had crustacean allergy - 9/10 with mollusc allergy were equally allergic to crustaceans
Turner et al 2011	167 children with definite clinical reaction to seafood	Convincing clinical history together with evidence of sensitisation based on skin testing/serum specific IgE, or positive food challenge	- 9/167 allergic to molluscs - 2/9 mollusc allergic children with clinical allergy to crustaceans
Sicherer et al 2004	Survey of the US population	Physician-diagnosed allergy or convincing history of allergy	- 41/303 with shellfish allergy reported allergy to both 1 or more crustaceans and 1 or more molluscs - 14% with crustacean allergy reported a mollusc allergy - rate of reactions to multiple molluscs: 49% - rate of reactions to multiple crustaceans: 38%

The FAISAG considered that the sequence similarity between crustacean and mollusc tropomyosin provides a theoretical basis for cross-reactivity but that overall the available data suggest that the extent of cross-reactivity is likely to be low. It was noted that clinical advice to patients with crustacean allergy regarding mollusc allergy generally varies between clinical practices. [Advice on seafood allergy](#) for patients, consumers and carers issued by the Australasian Society of Clinical Immunology and Allergy (ASCIA) states that while those allergic to seafood from one group (e.g. crustaceans) can usually tolerate those from another (e.g. molluscs), this cannot be guaranteed without specific allergy testing.

**Conclusion**

There is a theoretical basis and some evidence of cross-reactivity or co-sensitisation between molluscs and crustaceans based on serological testing, self-reporting and clinically diagnosed allergy. However, overall the available data suggest that the extent of clinically relevant cross-reactivity is likely to be relatively low.

FAISAG members noted that the clinical advice provided to patients with crustacean allergy regarding consumption of molluscs is likely to vary between clinical practices. ASCIA advice states while those allergic to seafood from one group (e.g. crustaceans) can usually tolerate those from another (e.g. molluscs), this cannot be guaranteed without specific allergy testing.



## 3 Tree nut allergy

### 3.1 Background

The Code requires food manufacturers to declare on labels the presence of 'tree nuts, other than the fruit of the palm *Cocos nucifera*'. The W1070 Review concluded that the problem with using the term 'tree nuts' in allergen declarations is that it is a collective term, and could be referring to certain nuts that are not associated with a food allergy. As such, there is no means of identifying a specific allergen source (e.g. almond or cashew nut) without further information on the food label.

Ordinarily more information on the relevant allergen would be available from the ingredient list. However, the W1070 Review identified that such information is not always provided. This could cause consumers to make overly restrictive food choices.

The W1070 Review therefore recommended that the requirements in the Code need to be clear on what individual tree nuts are to be declared as allergens on food labels.

During the W1070 Review, stakeholders noted that some tree nuts not included in the Code definition of tree nuts, such as nangai nuts, shea nuts and illipe nuts, may be associated with allergic reactions. In addition, a submission was received regarding how the current exemption for declaring coconut was meant to operate, given that there are species of coconut other than *Cocos nucifera*.

To be able to develop requirements for labelling of tree nuts, FSANZ needs to know which particular tree nuts are associated with allergies in Australia and New Zealand, and how cross-reactivity occurs across different tree nuts. The FAISAG previously gave advice on this matter in 2010, noting that nine tree nuts are important allergens that should be labelled. These tree nuts are: almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts.

For the current proposal it was considered timely to review whether any new information has become available indicating a need to change this list.

The following risk assessment questions have been considered:

- Is there any new information that would change the 2010 FAISAG advice on which tree nuts should be labelled?
- Is there any evidence of particular tree nuts not showing cross-reactivity?
- Are nangai nuts, shea nuts and illipe nuts associated with food allergy?
- Can consumption of other coconut species cause allergic reactions (e.g. *Lodoicea maldivica*, *Bactris gasipaes*, *Bactris minor*, *Borassus flabellifer*, *Salacca edulis*)?

### 3.2 Responses to risk assessment questions

#### 3.2.1 Is there any new information that would change the 2010 FAISAG advice on which tree nuts should be labelled?

##### ***Tree nuts implicated in Australian and New Zealand allergies***

There are a number of reports of food allergy and/or anaphylaxis to various tree nuts in Australia, with only a small number of reports available relating to New Zealand. However, many studies of allergy prevalence or anaphylaxis cases are limited in that reactions to 'tree nuts' are reported, without further indication of the specific types of nut involved.

A summary of information relating to specific tree nuts is provided below.

### *Estimates of prevalence of tree nut allergy in Australia and New Zealand*

The prevalence of tree nut allergy in Australian children, based on skin prick test responses, was estimated as 0.76% for almonds, Brazil nuts, cashew nuts, hazelnuts and walnuts combined (Hill et al 1997). The highest estimated prevalence was for cashew nuts, at 0.33%, and lowest for almonds at 0.02%. Other tree nuts were not assessed in this study.

Peters et al (2017) reported an update on the estimated prevalence of food allergy at age 1 and 4 years among children enrolled in the Australian HealthNuts study<sup>1</sup>. The prevalence of allergy to specific tree nuts was not reported, but oral food challenges in children aged 4 years indicated that cashew was the most commonly presenting new food allergy at this age, occurring in 48 of the 5276 (0.9%) children included in the study cohort.

Tree nuts were recently reported to be one of the most common food allergens among a population-based sample of 10- to 14-year old adolescents in Melbourne, Australia (Sasaki et al 2017). The prevalence of clinic-defined current tree nut allergy was 2.3%, and the tree nut with the highest prevalence was cashew nuts (1.6%). Other tree nuts associated with clinic-defined food allergy were pistachio (1.0%), walnut (0.7%), hazelnut (0.7%), macadamia (0.2%), pecan (0.2%), almond (0.1%), Brazil nut (0.1%) and pine nut (0.1%).

### *Clinical cases of tree nut allergy reported in Australia and New Zealand*

A retrospective review of 213 children presenting with peanut or tree nut allergy in Brisbane, Australia, over a 42 month period found that 27 (12.6%) had cashew allergy (Davoren and Peake 2005). Nine (4.2%) children had allergy to other nuts: two each to almond and pecan, one each to hazelnut and walnut and three to a mixture of nuts (mixed beer nuts, a mixture of Brazil and cashew and a fruit and nut chocolate bar). While peanut allergy was more common than tree nut allergy, anaphylaxis following ingestion of cashew nut or other nuts (86.4% and 62.5% respectively) was more common than anaphylaxis following peanut ingestion (31.7%).

In a 5 year retrospective review of children presenting with anaphylaxis at the Royal Children's Hospital in Melbourne, Australia, food was found to be the most common cause, linked to 85% of cases (de Silva et al 2008). Tree nuts caused 17% of food reactions, with the majority caused by cashew nuts (13%). Other tree nuts accounting for anaphylaxis episodes were walnut (2%) and macadamia (2%).

A recent review of data relating to anaphylaxis fatalities in Australia found that among 147 verified anaphylaxis deaths recorded in the National Coronial Information System between 2000 and 2013, 22 cases were considered to be due to food consumption (Mullins et al 2016). Of these 22 cases, one was linked to walnut, one to 'peanut, pistachio' and one to 'tree nuts (cashew, pistachio, pecan, walnut)'.<sup>1</sup>

Positive oral food challenge responses to cashew nut, hazelnut, walnut, pine nut and pecan nut were reported in a cohort of Australian children aged 4 years (Peters et al 2017).

A case report of fatal allergic reaction in an 8 year old child in New Zealand following cashew nut ingestion was reported by Sinclair (2013). An incident of anaphylaxis following consumption of marking nut (*Semecarpus anacardium*) in Australia has recently been reported (Fok et al 2016).

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<sup>1</sup> The [HealthNuts](#) study is a comprehensive population-based study of food allergy with objective measurement of true food allergy.

## *Nuts not previously identified as common allergens by the FAISAG*

A recent report on food allergy by the US National Academy of Sciences (NAS) notes that under Canadian labelling requirements nine tree nuts are required to be listed: almonds, Brazil nuts, cashews, hazelnuts, pecans, pistachios, pine nuts, macadamias and walnuts (NAS 2017). A US Food and Drug Administration (USFDA) guidance document includes these nine tree nuts plus an additional 10, including five of the seven additional nuts listed in Schedule 22 of the Australia New Zealand Food Standards Code (the Code): beech nuts, chestnuts, coconuts, hickory nuts and pili nuts. The NAS report states that scientific and clinical evidence supporting the inclusion of the additional 10 tree nuts in the US report is lacking.

Literature searches did not identify any papers relevant to food allergy for five of the seven additional nuts listed in the Code. For hickory nuts, 13 papers were retrieved (those relevant to food allergy focused on pecan, a species of hickory). Several papers on chestnut allergy were retrieved, but no reports of cases of chestnut allergy in Australia or New Zealand were identified.

The FAISAG did not consider there was a need to amend the Group's previous advice regarding nuts of clinical significance in Australia and New Zealand. Allergic responses are seen to all nine of the tree nuts identified (almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts).

Based on FAISAG Members' experiences and information in the literature, some cases of anaphylaxis have been seen following consumption of other tree nuts such as chestnuts, candle nuts and marking nuts. However, the FAISAG considered that these are rare and labelling of these tree nuts was not warranted at the current time.

### **Conclusion**

Clinically defined food allergy, clinical cases or positive responses to oral food challenges in Australia and/or New Zealand have been reported in the scientific literature for all nine of the tree nuts previously identified as being important allergens.

No new information indicating a need to amend the list of tree nuts was identified. While a small number of cases of anaphylaxis have been seen following consumption of other tree nuts such as chestnuts, candle nuts and marking nuts, these are very rare.

### **3.2.2 Is there any evidence of particular tree nuts not showing cross-reactivity?**

Serological cross-reactivity to allergens in different tree nuts, or between tree nut and peanut allergens, has been reported and provides a theoretical basis for cross-reactivity between nuts.

Clinical studies demonstrate that rates of allergy to more than one nut are lower than rates of sensitisation, and serological measurements of sensitisation are not always of clinical relevance. For example, 14 of 19 patients (74%) who had never eaten a tree nut, but were sensitised to tree nuts as measured by serum IgE, passed double-blind, placebo-controlled food challenges (DBPCFC) with the nut causing sensitisation (Fleischer et al 2005). Nevertheless, a number of clinical studies confirming that cross-reactivity and/or co-allergy among certain nuts are of clinical significance are also available. Clinical reactions to more than one nut have been reported in up to one third of tree nut allergic individuals.

Given that measures of sensitisation over predict clinical cross-reactivity, debate is ongoing in the scientific literature as to whether all tree nuts should be avoided by individuals with tree nut allergy, particularly in the case of previously tolerated tree nuts to which a positive IgE or skin prick result is found (Couch et al 2017; Eigenmann et al 2017). In a review of fatal anaphylaxis incidents in the UK from 1992 – 1998 it was suggested that at least three fatalities were most probably due to consumption of a nut that had not previously caused a reaction (Pumphrey 2000).

Allergy to multiple nuts may be a result of similar amino acid sequences or the presence of closely related epitopes, such as the cross-reactivity and high sequence homology found between the pistachio and cashew allergens rPis v 3 and rAna o 1, respectively (Willison et al 2008). It has been suggested that serological and clinical cross-reactivity between non-related nuts such as peanuts and tree nuts may be due to reactivity between similar storage proteins such as vicillins (Eigenmann et al 2017).

### ***Cross-reactivity among specific nuts***

Several groups of strongly cross-reactive tree nuts have been identified based on measures of IgE inhibition and antisera recognition (Goetz et al 2005). While these groupings suggest that some nuts may be more strongly cross-reactive than others, it has not yet been demonstrated that there is a lack of clinical cross-reactivity or co-sensitisation between any specific nut types.

The strongest cross-reactivity among tree nuts appears to follow botanical family groups (Goetz et al 2005), although cross-reactions that do not correlate with taxonomic relationships have also been reported (de Leon et al 2003). Walnut, pecan and hazelnut have been reported to form a group of strongly cross-reactive tree nuts based on serologic cross-reactivity, with hazelnut, cashew, Brazil nut, pistachio and almond forming a group of moderately cross-reactive tree nuts (Goetz et al 2005). The strongest serologic cross-reactions are reported for walnut and pecan in the family *Juglandaceae* and cashew and pistachio in the family *Anacardiaceae* (Goetz et al 2005, Hasegawa et al 2009, Maloney et al 2008, Uotila et al 2016, Willison et al 2008).

Almond, hazelnut and peanut sensitisation have been reported to be clustered as a group (Uotila et al 2016), and serologic cross-reactivity between almond, Brazil nut, hazelnut and peanut has been observed (de Leon et al 2003). A third cluster of sensitisation to other nuts, including pecan, walnut and macadamia, was identified by Uotila et al (2016).

It has been suggested that individuals with pine nut allergy generally have a low rate of IgE cross-reactivity with other commonly eaten nuts (reviewed by Cabanillas and Novak 2015). IgE binding to proteins from *Pinus pinea* nuts has been shown to be inhibited by proteins from nuts from another pine nut (*P. cembra*), but not by hazelnut or peanut (Vermuelen et al 1996), although another study reported inhibition of IgE binding to pine nut by almond (de las Marinas et al 1998). Pin p 1, a 2S albumin, is a major allergen in pine nut. Pin p 1 has been shown to have high sequence homology with 2S albumins from other species of gymnosperms, to which pine nuts belong, and low homology with 2S albumins from angiosperms, to which all other nuts belong (Cabanillas et al 2016). Gymnosperms separated from angiosperms about 100 million years ago and this evolutionary split has been proposed as an explanation for a lack of, or low cross-reactivity between pine nuts and other tree nuts (Cabanillas and Novak 2015).

While these studies are suggestive of the possibility that cross-reactivity between pine nuts and other tree nuts is low or even absent, there is currently a lack of clinical data to confirm this hypothesis. Recent data collected in a study of food allergy in 10- to 14-year old adolescents in Melbourne indicate that of six children with clinic-defined pine nut allergy, five had allergy to peanuts and/or multiple tree nuts (K Allen, pers. com.)<sup>2</sup>. No assessment of cross-reactivity is available for these children.

### ***Studies based on self-reports of clinical reactions***

Among 54 children with a convincing history of an acute allergic reaction to tree nuts, 34 (63%) had experienced a reaction to only one type of nut, 12 (22%) to two types and 8 (15%) to three or more

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<sup>2</sup> Professor Katie Allen, Director Population Health Research Theme, Gastro & Food Allergy Group, Population Health, Murdoch Research Institute, Melbourne, Australia. 24.10.2017

types (Sicherer et al 1998). Walnut, almond, pecan and cashew were the most common tree nuts responsible for reactions.

In a study of 784 children with a history of tree nut and/or peanut allergy 175 (22%) reported clinical reactions to multiple nut types (Clark and Ewan 2005). The proportion of children allergic to more than one nut type increased with age, from 2% among children presenting at age 0-2 years to 47% at 14 years of age.

#### *Studies based on oral food challenges*

Positive DBPCFC responses were seen in 19 challenges administered to 14 children evaluated for adverse reactions to nuts (Bock and Atkins 1989). Twelve patients reacted to a single nut each, one patient reacted to two nuts and the other reacted to five nuts.

Ball et al (2011) performed open food challenges on 145 patients diagnosed as allergic to peanuts or tree nuts. Five of 13 patients (38.4%) with tree nut allergy and positive skin prick test reactions to other tree nuts and/or peanuts reacted to oral challenges with those nuts, while 3 of 38 patients (7.9%) with negative skin prick tests to the challenge nuts reacted to oral challenges (Ball et al 2011).

Couch et al (2017) reported a retrospective review of the outcome of open tree nut oral food challenges conducted at the University of Michigan between 2007 and 2015. Among patients with tree nut allergy, 24% of 67 oral food challenges with another tree nut to which they were sensitised resulted in an allergic reaction. In patients with tree nut sensitisation but no history of allergy, 9% of 65 oral food challenges resulted in positive responses.

FAISAG Members noted that cross-reactivity or co-allergy to different tree nuts is commonly seen. In one Member's experience around two thirds of patients are sensitive to more than three nuts. Cross-reactivity between cashew and pistachio is commonly seen, as is cross-reactivity between pecan and walnut. [Advice on peanut, tree nut and seed allergy](#) issued to patients, consumers and carers by ASCIA notes that with few exceptions (e.g. most people allergic to cashew are also allergic to pistachio) it is not possible to reliably predict the likelihood of allergy to seed or nut-like food without allergy testing to that particular food.

#### **Conclusion**

Clinical responses to more than one tree nut have been reported to occur in up to a third of allergic individuals, and the incidence of reactions to multiple nuts may be even higher based on FAISAG Members' experience. Some groups of strongly cross-reacting tree nuts have been identified, with the strongest reactions being found between: a) walnut and pecan; and b) cashew and pistachio.

Clinical confirmation of a lack of cross-reactivity between specific tree nut types has not been reported. It has been suggested that pine nuts may not cross-react with other tree nuts, however this has not been confirmed clinically to date.

#### **3.2.3 Are nangai nuts, shea nuts and illipe nuts associated with food allergy?**

Stakeholders have mentioned that nangai nuts, shea nuts and illipe nuts may be associated with allergic reactions.

No conclusive evidence of an association between consumption of nangai, illipe or shea nuts and clinical allergy has been identified to date. A search for 'Nangai nut AND allergy' retrieved three results, two of which were review articles citing the other paper, a study by Sten et al (2002). In this study 11 of 64 patients with known pollen allergy were found to have specific IgE against nangai nut. Among 36 patients with pollen allergy, 18 had a positive response to nangai in a histamine release, skin prick test or radioallergosorbent test. Twelve of the 18 patients with a positive nangai specific test result had an open food challenge with nangai, with three having a positive reaction.

However, DBPCFCs were conducted with two of these individuals and no positive response was observed in these tests.

A further paper was identified from a review of oil derived from nangai nuts by the Australian Therapeutic Goods Administration (TGA 2004). In this study RAST inhibition tests using nangai nut extracts were conducted with sera from 20 individuals with positive RAST responses to peanut, hazelnut, cashew nut or pistachio nut (five of each). Significant inhibition was observed in one out of five tests for hazelnuts and cashew nuts, and in all five cases with pistachio nut. No significant inhibition was found against peanut. Although this study only evaluated sensitisation, the authors hypothesised that it may indicate a risk of cross-allergenicity between nangai nuts and pistachio (Frémont et al 2001).

A search for 'Shea nut AND allergy' retrieved one result. Chawla et al (2011) found that extracts of shea nut and shea butter contain very low levels of water/salt soluble protein compared with peanuts and other tree nuts such as cashew, pistachio and Brazil nuts. In addition, no IgE binding to shea nut or shea butter was detected using sera from peanut and/or tree nut allergic individuals. It was suggested that this finding could explain why there are no reports of ingestion or contact-related reactions to shea butter in individuals with nut allergy.

A PubMed search for 'Illipe nut AND allergy' retrieved no results.

## **Conclusion**

Evidence relating to the allergenicity of less commonly consumed tree nuts is currently lacking. Given that these nuts are unlikely to be widely used in processed foods and may only be consumed by small numbers of individuals, there is some uncertainty about whether these tree nuts would be likely to be significant allergens under conditions of more widespread use.

### **3.2.4 Can consumption of other coconut species (e.g. *Lodoicea maldivica*, *Bactris gasipaes*, *Bactris minor*, *Borassus flabellifer*, *Salacca edulis*) cause allergic reactions?**

*Lodoicea maldivica* is a rare plant endemic to the Seychelles, and is considered to be endangered (Fleischer-Dogley et al. 2011). The fruit are commonly referred to as coco de mer or sea coconut. PubMed searches for '*Lodoicea maldivica* AND allergy', 'coco de mer AND allergy' or "sea coconut" AND food allergy' produced no results.

*Bactris gasipaes*, also referred to as peach palm, has been consumed by people in the Americas for centuries (Galluzzi et al. 2015). PubMed searches for '*Bactris gasipaes* AND allergy' and "peach palm" and allergy' retrieved no results.

*Bactris minor* is also known as *Bactris guineensis*, and the fruits are referred to as Corozo fruit. This tropical fruit is found in Colombia, where it is used to prepare juices or alcoholic drinks (Osorio et al. 2010). PubMed searches for "*Bactris minor*" AND allergy', "*Bactris guineensis*" AND allergy' and 'Corozo AND allergy' did not retrieve any relevant results.

*Borassus flabellifer*, also referred to as the palmyrah palm, is native to the Indian subcontinent and Southeast Asia. In some areas it is a source of a number of foods including fruit, sugar and liquor as well as flour derived from young plant shoots (Chakraborty et al. 1998; Devi et al. 1985). PubMed searches for '*Borassus flabellifer* AND allergy', or for 'palmyrah palm AND allergy' did not retrieve any papers relevant to food allergy, although a small number of papers relating to respiratory allergy associated with airbourne pollen from *B. flabellifer* were identified (e.g. Chowdhury et al. 1999; Chakraborty et al. 1998).

The fruits of *Salacca edulis* are known as snake fruit. PubMed searches for "*Salacca edulis*" AND allergy' and for "snake fruit" AND allergy' did not retrieve any results.

In addition, the [Allergen Online](#) database of proven or putative allergens (food, airway,

venom/salivary and contact) does not include proteins from any of these plant species.

## **Conclusion**

No evidence was identified indicating an association between consumption of *Lodoicea maldivica*, *Bactris gasipaes*, *Bactris minor*, *Borassus flabellifer* or *Salacca edulis* and food allergy, although several of these species are consumed as foods overseas.

# **4 Cereal allergy**

## **4.1 Background**

The Code currently requires a declaration on food labels of 'cereals containing gluten (namely wheat, barley, rye, oats or their hybrids)'. As with tree nuts, the problem with the use of this term in allergen declarations is that it is a collective term for food ingredients that may cause separate allergies. This requirement is also unclear on whether the presence of gluten or the cereal should be declared.

The W1070 Review identified that the term 'gluten' is being used regularly in the 'contains' summary statement on foods, without any additional reference to the individual cereal in the statement and sometimes not even in the ingredient list. This labelling practice was seen to be unhelpful to those with a cereal-specific allergy (primarily wheat allergy).

The following risk assessment questions have been considered:

- Are rye, barley and oats only associated with gluten intolerance, or are these also food allergens? If so, what is the prevalence/clinical significance of these allergies in Australia and New Zealand?
- Do wheat allergic individuals react to hybrid strains of wheat and other cereals (e.g. triticale)?

## **4.2 Responses to risk assessment questions**

### **4.2.1 Are rye, barley and oats only associated with gluten intolerance, or are these also food allergens? If so, what is the prevalence/clinical significance of these allergies in Australia and New Zealand?**

Wheat, rye, barley and oats have all been reported to cause IgE mediated allergic reactions which can be due to ingestion or inhalation, with wheat allergy being the most commonly reported (EFSA 2014; University of Portsmouth 2013). Food allergy to wheat develops most commonly in infants and frequently resolves by adolescence. However, no data are available on the natural history of barley, rye or oat food allergy (EFSA 2014).

Wheat proteins can be classified into water-soluble albumins, salt-soluble globulins, ethanol-soluble prolamins (which include gliadins) and acid-soluble glutenins (EFSA 2014, FSANZ 2010). The gliadins and glutenins form the gluten fraction. In barley and rye the prolamins are called hordeins and secalins, respectively (Cianferoni 2016).

Several studies have reported positive allergic responses to food challenges with barley, rye and/or oats in children or adults (Armentia et al 2002, Armentia et al. 2008, Jones et al. 1995, Pourpak et al 2005, Räsänen et al. 1994). In the majority of these studies individuals were confirmed as not having coexisting coeliac disease, while Pourpak et al did not report on the coeliac status of their study participants. Jones et al. (1995) found that among 31 patients who had positive challenge responses to wheat, barley, rye, oat, rice or corn, 80% responded to one grain only, while 10% had positive challenge responses to two grains and the remaining 10% had responses to four grains.



### *Food allergens in barley, rye and oats*

The World Health Organization and International Union of Immunological Societies (WHO/IUIS) Allergen Nomenclature database lists the following food allergens in barley and rye. No oat allergens are listed in the database.

Barley:

- Profilin (Hor v 12; molecular weight [MW] 14)
- $\alpha$ -amylase inhibitor BMAI-1 precursor (Hor v 15; MW 14.5)
- $\alpha$ -amylase (Hor v 16; MW unspecified)
- $\beta$ -amylase (Hor v 17; MW unspecified)
- $\gamma$ -hordein 3 (Hor v 20; MW 34)

Rye:

- $\gamma$ -secalin (Sec c 20; MW 70 kDa)

$\gamma$ -hordein 3 in barley and  $\gamma$ -secalin in rye, as well as a 35 kDa  $\gamma$ -secalin in rye, are ethanol-soluble prolamins and part of the gluten fraction of barley and rye. They have been found to cross react with wheat  $\omega$ -5 gliadin, a major allergen in wheat dependent exercise induced anaphylaxis (WDEIA) as well as other forms of wheat allergy (Palosuo et al 2001).

$\alpha$ -amylase inhibitor BMAI-1 precursor is a salt-soluble protein (Barber et al 1989) and is a non-gluten protein in barley.

### *Non-IgE mediated food allergy*

Eosinophilic oesophagitis (EoE) is a non-IgE mediated food allergy reaction characterised by oesophageal eosinophilia with symptoms including vomiting, feeding difficulties and food impaction. Wheat has been identified as one of the most common triggers of EoE (Cianferoni 2016). Some clinicians have suggested that patients with EoE should also exclude barley and rye – and in some cases oats – from their diets due to concerns over potential cross-reactivity and/or cross-contamination with wheat. However, to date there are no studies available indicating whether there is any clinical benefit in doing so (Kliwer et al 2016).

### **Prevalence in Australia and New Zealand**

No studies relating to the prevalence of food allergy to barley, rye or oats in Australia or New Zealand were identified in searches of the scientific literature. Only limited information is available relating to prevalence overseas.

The FAISAG observed that they do see cases of rye and barley allergy but these are not common. The cases often occur in patients who also have wheat allergy. Oat allergy is very rare and problems are usually due to cross-contamination with other cereals. It was noted that most patients with wheat allergy can eat rye and barley. Clinical advice to patients with allergy to rye, barley or oats would generally be to avoid foods that contain gluten.

[Advice to patients, consumers and carers on dietary avoidance for wheat allergy](#) issued by ASCIA states that approximately 20% of individuals with wheat allergy may be allergic to other cereals such as barley, rye or oats, in line with the findings by Jones et al. (1995). ASCIA recommends that individuals with wheat allergy should ask their allergy specialist if they need to avoid all gluten containing foods or just wheat.

### **Conclusion**

Food allergy to barley, rye and oats is IgE-mediated and distinct from gluten intolerance. Several



studies have reported positive allergic responses to food challenges with barley, rye and/or oats in children or adults, and in most of these studies individuals were confirmed as not having coexisting coeliac disease. Gluten and non-gluten proteins have been identified as allergens in barley.

There is a lack of data regarding the prevalence of allergy to these cereals in Australia and New Zealand. FAISAG Members advised that they do see cases of rye and barley allergy, although these are not common. Oat allergy is very rare and problems are usually due to cross-contamination with other cereals.

#### **4.2.2 Do wheat allergic individuals react to hybrid strains of wheat and other cereals (e.g. triticale)?**

There is a general agreement that hybrid strains of wheat and other cereals such as triticale (a hybrid of wheat and rye) share antigenic potential with wheat (EFSA 2014). This is to be expected given that hybrid strains will contain some or all of the proteins present in the parent strains. Skoczowski et al. (2017) recently reported that sera from seven patients with wheat allergy had IgE reactivity to gluten and/or non-gluten proteins in two wheat hybrids, including one hybrid strain which did not contain any  $\omega$ -gliadins.

No information regarding the prevalence and/or clinical significance of hybrid strains for wheat allergic individuals in Australia and New Zealand was identified. FAISAG Members noted that patients with wheat allergy are advised to avoid hybrids.

## **5 Overall conclusions**

Three mollusc classes (bivalves, gastropods and cephalopods) have been implicated in cases of food allergy. Although there are few published data specifically regarding the prevalence of mollusc allergy in Australia and New Zealand, FSANZ's Food Allergy and Intolerance Scientific Advisory Group (FAISAG) has advised FSANZ that mollusc allergy is of clinical significance in the two countries.

There is some evidence of cross-reactivity or co-sensitisation between molluscs and crustaceans based on serological testing, self-reporting and clinically diagnosed allergy. However based on available data the extent of clinically relevant cross-reactivity is likely to be relatively low.

FAISAG previously advised FSANZ that nine tree nuts are important allergens: almonds, Brazil nuts, cashews, hazelnuts, macadamias, pecans, pine nuts, pistachios and walnuts. Clinically defined food allergy, clinical cases or positive responses to oral food challenges in Australia and/or New Zealand have been reported for all of these tree nuts. Clinical responses to more than one tree nut have also been reported to occur in up to a third of allergic individuals, and the incidence of reactions to multiple nuts may be even higher based on the advice of FAISAG.

There is little evidence relating to the allergenicity of less commonly consumed tree nuts, and FAISAG considered that the available information did not indicate a need to amend its previous advice on significant tree nut allergens. However these nuts are currently unlikely to be widely used in processed foods and may only be consumed by small numbers of individuals. Therefore this conclusion may need to be revised if use patterns change significantly.

Food allergy to barley, rye and oats is IgE-mediated and distinct from gluten intolerance. Several studies have reported positive allergic responses to food challenges with barley, rye and/or oats in children or adults, and in most of these studies individuals were confirmed as not having coexisting coeliac disease. Gluten and non-gluten proteins have been identified as allergens in barley.

There is little data on the prevalence of allergy to these cereals in Australia and New Zealand. The FAISAG advised FSANZ that they do see cases of rye and barley allergy, but these are not common. Oat allergy is very rare and problems are usually due to cross-contamination with other cereals.

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