

Dietary management of peanut and tree nut allergy: what exactly should patients avoid?

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Summary

Peanut and tree nut allergies are the commonest cause of life-threatening food-allergic reactions and significantly affect quality of life in children and their families. Dietary nut avoidance and provision of emergency medication is currently the mainstay of treatment. Nut avoidance has consequences on both quality of life and nutrition. We review the terminology that may cause confusion and lead to unnecessary dietary restrictions. In peanut or tree nut-allergic children, introduction of specific nuts to which the child is not allergic may improve quality of life and should be considered in patients with multiple foods allergies, vegan or ethnic-specific diets, in whom nuts are an important source of protein. Nut-allergic consumers do not just need to avoid foods containing nuts as an ingredient, but also contend with pre-packed foods which frequently have precautionary allergen labelling (PAL) referring to possible nut contamination. Although the published rate of peanut contamination in 'snack' foods with PAL (see Box 1) ranges from 0.9–32.4%, peanut contamination in non-snack items with PAL is far less common. We propose that in some peanut-allergic patients (depending on history of reactivity to trace levels of peanut, reaction severity, other medical conditions, willingness to always carry adrenaline, etc.), consideration may be given to allow the consumption of non-snack foods containing PAL following discussion with the patient's (and their family's) specialist. More work is needed to provide consumers with clearer information on the risk of potential nut contamination in pre-packed food. We also draw attention to the change in legislation in December 2014 that require mandatory disclosure of allergens in non-pre-packed foods.

Background

Acute allergic reactions to peanut and tree nuts have increased in the UK [1, 2], USA [3, 4] and Australia, particularly in children [5]. Peanut allergy is characterised by severe reactions [6, 7] and is the commonest cause of life-threatening anaphylaxis [8, 9]; this may be due to the high prevalence of peanut allergy [2, 4, 5], the increased allergenicity that may occur through peanut processing (predominantly roasting) [10] and a higher rate of cross-contamination due to more widespread use of peanuts in processed and restaurant foods

[11]. Data suggest that cashew and pistachio are also associated with severe allergic reactions, amongst other tree nuts [12]. Nut allergies result in a significant impact on a patient and their family's quality of life [13–15]. Although there are exciting developments in research into the prevention [16] and treatment of established peanut allergy [17, 18], at present dietary avoidance remains the mainstay of management, with provision of written emergency plans and rescue medication.

Consequences of dietary avoidance

Nuts have been part of the diet throughout human evolutionary history [19]. Dietary avoidance has nutritional

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consequences [20], and dietary restrictions in children with foods allergies can compromise nutrition and growth [21]. Nut avoidance is particularly difficult for vegetarian/vegans or those with an ethnic-specific diet, in whom nuts and seeds are an important source of protein [22–24]. A variable proportion of peanut-allergic subjects react to related legumes (e.g. soya, lentil, lupine and chickpea) [25–28]. Nuts may be extremely useful in children with multiple food allergies; such children can benefit from specific almond, hazelnut or coconut ‘milk’ drinks, many of which are fortified with calcium and vitamins.

Nut avoidance can be difficult: pre-packed foods frequently have precautionary advisory labelling (PAL) referring to possible nut contamination [29]. PAL (perceived as warning labels by consumers and many healthcare providers) is frequently cited as contributing to anxiety in food allergy [30, 31]. In research sponsored by the UK Food Standards Agency (FSA), the Anaphylaxis Campaign reported that 69% of cereals and 56% of confectionery (e.g. chocolates) were labelled as containing ‘traces’ of nuts, despite none listing peanut or tree nuts as an ingredient [32]. Shopping for a nut-allergic person took almost 40% longer and cost an average of 11% more. Thus, nut avoidance has obvious implications for consumer choice and quality of life; studies have indeed shown that parents of peanut-allergic children have significantly more disruption in their daily activities and familial/social life than for other chronic diseases [13].

Are we able to predict those individuals more at risk of severe food-allergic reactions?

One approach to risk management in food allergy is an attempt to assess the risk of severe, potentially life-threatening allergic reactions in a given individual. This needs to take into consideration a number of factors: the likelihood of exposure (for example, risk of cross-contamination), the hazard resulting from exposure and the availability of rescue medication (and a person's willingness and ability to use this appropriately). Are there any data which can be used to inform as to whether some individuals are more at risk of severe reactions than others?

Unfortunately, severity of future peanut and tree nut-allergic reactions is difficult to predict. While there are certain risk factors which define those at higher risk of severe reactions, one cannot define patients who are low risk. Over half of food allergy-related deaths in a UK case series from Pumphrey *et al.* between 1999 and 2006 were in patients whose previous reactions were considered mild [9]. Vander Leek *et al.* followed up 83 children (under age 4 years) with peanut allergy and found that 60% had accidental exposures (at an average

of one every 3 years). Of the children with initially non-life-threatening reactions, 44% had at least one subsequent potentially life-threatening reaction [33]. In a cohort of 785 nut-allergic children in the UK, 14% (114/785) had subsequent reactions following diagnosis, of which 70 were due to ingestion, equating to an annual incidence of 2.0%. In those with prior mild reactions, 14% (10/70) experienced subsequent anaphylaxis [34]. More recently, Nguyen-Luu *et al.* reported 147 accidental reactions over 1175 patient-years; this equated to an annual incidence rate of 12.5%, although only 65% were due to ingestion [35]. The criteria used to grade severity in this study included a ‘moderate’ category which included both anaphylactic symptoms (e.g. breathing difficulties) and angioedema, which many clinicians would classify as mild. Thus, it was not possible to tease out the rate of anaphylaxis after an initial mild reaction. Risk factors for food-related anaphylaxis have been reviewed elsewhere [36] and are summarised in Table 1. A recent Swedish study reported that pollen-allergic children were more likely to be admitted with food-induced anaphylaxis during the tree-pollen season compared with the rest of the year; thus, severity may depend on cumulative allergen load [37].

Reviews of fatal (pea)nut-allergic reactions have reported risk factors including asthma (even well controlled), location of exposure remote to the home environment and non-timely delivery of adrenaline (although mortality is not prevented by early adrenaline alone) [8, 9, 38]. Many of these factors are only of limited utility in practice: while asthma is a risk factor for fatal anaphylaxis, in that 90% of fatalities occur in subjects with asthma [9], up to 50% of peanut-allergic individuals have asthma [39] yet almost none will experience a fatal food-allergic reaction; thus, asthma in itself is not a strong predictor for fatal peanut anaphylaxis [40]. The majority of fatal reactions occur outside the home environment, following exposure to allergens in non-pre-packed food items such as those sold in restaurants. Thus, a more cautious approach is advisable in restaurants and similar catering establishments; the recognition of this risk has prompted the inclusion of foods sold in these outlets in new European legislation on allergen disclosure which became effective in December 2014 [41].

It is often assumed that an individual with a history of a significant reaction to a very small amount of peanut has a higher risk for future anaphylaxis; however, this does not appear to be the case. Taylor *et al.* analysed 286 double-blind, placebo-controlled food challenges (DBPCFC) in peanut-allergic individuals presenting to an allergy service [42]. Of note, in contrast to most other series of DBPCFC, the authors did not exclude those with a prior history of a severe aller-

Table 1. Factors associated with life-threatening reactions to peanut [8, 9, 38]

Factors associated with increased risk	Factors associated with low risk
Prior anaphylaxis to the same food	?
Teenagers and younger adults [110, 115]	?
Comorbidities (asthma, cardiovascular disease, mastocytosis) [110, 116]	?
Concurrent use of medications (e.g. non-selective beta-blockers and non-steroidal anti-inflammatory drugs)	?
Exercise	?

gic reaction. While the authors did not seek to assess differences in triggering dose (threshold) between those with and without a history of prior anaphylaxis as a primary outcome, they found no difference in the triggering dose between these two groups, implying that those who have reacted to minimal doses of peanut are no more likely to have severe life-threatening symptoms, a finding subsequently confirmed elsewhere [43]. Those with a history of severe reactions thus appear to include both individuals reactive to minimal doses of peanut and also others who develop symptoms only after comparatively large exposures to peanut. However, it is difficult to determine the dose of peanut causing historical reactions, and further studies are needed to confirm the lack of association found in these studies.

There have been recent advances in the diagnosis of peanut allergy, in particular the use of component resolved diagnostics (CRD), in which antibodies against specific components of an allergenic food are quantified. Studies have sought to determine the correlation between specific components and true clinical reactivity (rather than sensitisation alone). Ara h 2 has been shown to be superior to conventional allergy tests in predicting clinical reactivity in some studies but not in others [5, 44–47]. It has been suggested that Ara h 2 may also predict clinical severity in those with a *primary sensitisation* (evidence of specific IgE to Ara h 1, 2 or 3) to peanut [48], but there is little evidence for this in the literature, as reviewed recently by Sicherer and Wood [49]. However, patients with exclusive Ara h 8 and Cor a 1 reactivity, thought to indicate primary sensitisation to tree pollen with resulting cross-reactivity to peanut and hazelnut, respectively, are more likely to have mild reactions [50–52]. Detection of IgE to Ara h 9 and Cor a 9 (lipid transfer proteins) is associated with clinical severity in Spain [53–55], but the relevance of this to other geographical populations is

unknown. Promiscuity of IgE binding to intact peanut allergens [51, 56] and high diversity of IgE against specific regions (epitopes) of Ara h 1, 2 and 3 [57] have been related to severity of clinical symptoms; however, such diagnostic subtleties are not routinely available in clinical practice.

Terminology and uncertainty in nut allergy

The terminology used to describe peanuts and tree nuts can cause confusion and excessive avoidance practices. For example, it is common for some people to restrict foods whose name contains the word 'nut', for example **nutmeg**, **butternut** squash, **water chestnuts**, **palm nut**; these are not nuts and do not classically cause reactions in nut-allergic patients. A further common misconception occurs with fruits that have 'stones' which are perceived as resembling a nut kernel, for example peach, apricot and cherry. Almonds belong to the same genetic family as apricots and cherries, but cross-reactions to the fruit are rarely encountered. Nuts are 'hard' fruits [58] (*fruit a coque* in French) [59], which contain seeds, and nut-allergic patients rarely exhibit cross-reactivity to seeds in 'conventional' fruits, such as citrus fruits [60]. We are aware of reports of clinical cross-reactivity with apricot kernels (*armelline*), typically in patients with peanut and almond allergy. Confusingly, natural almond essence is generally produced from peach kernels (rather than almonds) and is thus tolerated by many almond-allergic individuals. However, for the most part, nut-allergic patients are able to eat fruit, unless they have co-existing pollen food syndrome [61] or are sensitised to lipid transfer proteins in peanut (Ara h 9) which can cross-react with similar proteins in fruits (e.g. peach, Pru p 3) [53], a situation found predominantly in Mediterranean countries.

Peanuts are referred to as 'ground nuts' or 'monkey nuts', which also causes confusion. In fact, peanuts are legumes and botanically quite distinct from other nuts which grow on trees. Pine nuts are considered to be seeds within the EU for labelling purposes, but as a nut in North America. In the USA, several additional products are considered tree nuts, including coconut, shea nut and lychee. Some of these are not tree nuts botanically: coconuts are not tree nuts but palms; lychee is a fruit and not a nut.

Another area of uncertainty is nut oils; the amount of protein in highly-refined ground (peanut) nut oil (also known as neutralised, bleached and deodorised – NBD) is negligible [62] and at least one study found this to be tolerated by peanut-allergic subjects at DBPCFC [63]. However, specialty, unrefined 'gourmet', 'aromatic' or cold pressed oils from both peanut and tree nuts still contain nut protein in sufficient amounts to sometimes trigger allergic reactions [63, 64]; such products are

best avoided. Notably, the European Food Safety Authority requires any product containing extracts from a peanut source to be labelled as containing peanut, even for highly purified peanut oil. This can create additional and potentially dangerous confusion, as a peanut-allergic individual accidentally exposed to a product labelled as containing peanut but having no reaction may assume their allergy has resolved.

Clinically relevant co-sensitisation and allergy in peanut allergy

A significant proportion of children with peanut and tree nut allergy are sensitised to sesame seed and have reported sesame seed allergy [65–67]. There are reports of cross-reactivity between poppy seed and both hazelnut and sesame [68, 69]; however, co-existence of (pea) nut allergy and other seed allergies (e.g. sunflower, pumpkin, mustard, millet and linseed) is poorly described in the literature. There are isolated reports of cross-reactive antibodies between coconut and certain tree nuts (hazelnut and walnut) and reports of clinical reactivity [70, 71]; however, another study found that children with peanut and tree nut allergy are not more likely to be sensitised or allergic to coconut than non-nut-allergic children [72]. Many assume that legumes (beans, peas, lentils, chick peas, pulses and soya) must also be avoided in peanut allergy. Although the rate of co-sensitisation between peanut and legumes is high, there are wide geographical differences in the rate of challenge-proven, co-existent allergy ranging from < 5% [25–27] in the US (related to soya) to 17% in Mediterranean countries (related to lentils, chickpeas, white beans and peas) [28]. Lupine flour (used in many parts of mainland Europe, predominantly in bakery products) also has marked variation in clinically relevant sensitisation depending on the geographical region, ranging from 4% in peanut-allergic children in the UK [73] to 35% in the Netherlands [74]. Fenugreek is a legume used in Indian style spiced food which shows high cross-reactivity with peanut [75], and severe reactions to fenugreek have been reported in peanut-allergic individuals [76].

Should a peanut-allergic individual avoid all tree nuts?

In vitro cross-reactivity between peanut and tree nuts is high (86%) [77]; however, coexistence of reported (questionnaire-based) peanut and tree nut allergy is lower (20–59%) [3, 66, 67, 78, 79]. Challenge-proven allergy is lower still: in a retrospective review, only 7 of 94 peanut-allergic children (7.4%) were found to be allergic to tree nuts at challenge, despite 31% having at least one positive skin prick test to a tree nut (almond, brazil nut, cashew nut, hazelnut and walnut) [22]. One

area of concern is that children with an allergy to peanut or a single tree nut may develop further nut allergies over time. In a study of 784 children, Clark and Ewan reported that while 2% of 0–2 year olds had multiple nut allergies, this proportion increased to 47% at age 14 years [34]. However, it is unclear as to the extent this observation was an artefact of the testing protocol, with younger children more likely to be tested to only the index nut compared to older children who are more likely to undergo testing to a wider panel of nut/seed allergens. On the basis of these data, it has been proposed that children with any nut allergy should avoid all nuts after diagnosis [34]. The rationale for this is that a child might eat a nut (which they might have previously tested negative to) for the first time and have an allergic reaction. There is also concern that young children and the general population might be unable to discriminate between different nuts. The other hypothetical concern is that exposure might cause development of an allergy to that nut in the future. However, one must ask whether introduction of other tree nuts into the diet of a peanut-allergic child might prevent the development of subsequent tree nut allergies. The usefulness, or indeed lack of adverse influence on the overall course of the allergy to nuts, of blanket nut avoidance has not been proven. Advice regarding the consumption of nuts in early childhood has recently been revised. The prevalence of peanut allergy more than doubled in 3–4 year old UK children born in 1989 (0.5%) vs. those born between 2001 and 2002 (1.2%) [2], and more than tripled in the US from 1997 (0.4%) to 2008 (1.4%) (self-reported peanut allergy) [4]. These time periods coincided with previous recommendations from the UK Department of Health (1998) [80] and American Academy of Pediatrics (2000) [81] that children with a parent or sibling with an atopic diseases should avoid peanuts until 3 years of age, although the impact of these recommendations is unclear [82, 83]. These observations, together with recent epidemiological studies [84, 85], have led to a change in guidance and imply that nut avoidance may not be helpful as a means of primary prevention [86–88].

Should nut-allergic patients avoid foods with precautionary allergen labelling?

European legislation mandates the disclosure of specific food allergens present in the ingredients of pre-packed foods, which is defined as food put into packaging prior to sale (usually at premises different to the one where the food is finally sold) and which cannot be altered without breaking the packaging. Many manufacturers provide advice as to the potential for unintentional contamination with allergens; while such advice is often based upon a thorough risk assessment by a man-

ufacturer with adherence to Good Manufacturing Practice (GMP), it is suspected that some manufacturers use PAL as an alternative to allergen risk management, circumventing the process of an actual allergen risk assessment. Furthermore, the absence of PAL does not indicate that a food is free of potential cross-contaminants. The use of PAL on pre-packed foods is voluntary and not mandated within existing legislation. This results in wide inconsistencies in labelling between manufacturers, within product categories and between different countries. The awareness of the hazards posed by allergenic foods has increased markedly within the food industry over the past 20 years but understanding is still far from complete. Foods can become contaminated with residues of allergenic foods at multiple points along the food chain including harvesting on farms, storage, transportation and during manufacture. Different products may be produced on the same equipment line, some containing allergenic products, others not. Many companies make efforts to clean shared equipment between product runs, but this is not uniform across manufacturers and the effectiveness of such approaches can be challenging to evaluate [89].

There are reports in the literature of potentially life-threatening reactions due to peanut contamination in cookie/biscuit products without PAL (at a time when one could argue that allergen awareness amongst food manufacturers was at a lower level) [90]. Relatively few studies have been conducted to evaluate the risks posed by allergen residues in pre-packed foods. Pele *et al.* analysed 544 products (cookie biscuits and chocolates) for peanut content from 10 European countries in 2006. While 108/333 (32%) of pre-packed foods with PAL had evidence of peanut contamination, the rate of contamination was still 52/211 (25%) for items without such a warning. The authors defined a level of 20 ppm as being indicative of significant contamination; using this cut-off, there was no significant difference in the frequency of peanut contamination between foods with PAL (55/333, 17%) vs. those without PAL (24/211, 11%) ($p > 0.05$) [91]. Put more simply, a peanut-allergic individual had a 1 in 6 chance of eating a cookie or chocolate with significant contamination where there was PAL vs. a 1 in 9 chance when eating an equivalent item with no PAL. Hazelnut could be detected in 76% of chocolates and 28% of cookie biscuits with PAL and in 50% of chocolates without PAL [91]. On the basis of this data, the presence of PAL was not indicative of contamination risk, or, to be provocative, the absence of PAL was not indicative of no or even low risk of contamination. Of note, member states of the EU pre-2004 (Germany, the Netherlands, Belgium) had higher levels of peanut contamination than those products produced in more recent member states (eastern European countries).

More recent data indicates a far lower rate of contamination for many allergens, particularly in pre-packed foods without PAL. A survey of US supermarket products reported detectable peanut contamination (> 2.5 ppm) in only 4.5% (5/112) of products with PAL, vs. 0/120 items without [92]; all of the contaminated items were snack items. This lower rate of contamination may reflect (1) the smaller number of snacks assessed (86 in the US study vs. 544 in the European study); (2) the tendency of European manufacturers to include nuts as an ingredient in cookie biscuits; (3) more reliable allergen disclosure on US food items than equivalent European products. A further US survey of 'nutrition' meal bars in 2010 found no significant difference in the frequency of detectable peanut in products with PAL for peanut (12/159; 7.5%) and those nutrition bars without mention of peanut on the label (2/49; 4%) [93]. Two Irish studies have assessed the frequency of peanut contamination of foods containing PAL. One commissioned by the Food Safety Authority of Ireland (FSAI) reported 5 of 75 (6.7%) products with PAL contained peanut (threshold not defined), compared to 2 of 106 (1.9%) products with no peanut allergen declared either in ingredients or on PAL [94]. A subsequent Irish study evaluated 38 pre-packed foods with PAL for peanut using a 2.5 ppm threshold, all of which were snack items [95]. They did not assess foods without PAL. Two (5.3%) were found to have peanut contamination (a chocolate bar and a cereal bar); taking into consideration the level of contamination and serving size, this translated into an estimated risk of 2.6 predicted reactions per 1000 eating occasions. In the USA, a further risk modelling was performed on the consumption of cereal/nutrition bars (a high-risk food) with PAL; the authors estimate a risk of between 2 and 10 predicted reactions per 1000 eating occasions, stating that this is most likely an overestimate of the actual risk [93].

Compared to the 2006 study by Pele *et al.* [91], it is possible that the risk of peanut contamination is reducing over time as awareness increases within the food industry; more studies are needed to evaluate this possibility. Indeed, the UK Food Standards Agency (FSA) recently commissioned a large study which analysed a total of 508 food products (including confectionery, snacks, pre-packed bakery items, chilled/frozen meals and desserts) for allergen (cow's milk, gluten, peanut and hazelnut) contamination [96]. Peanut contamination was found only in one product, a chocolate bar which had PAL equating to 1/110 (0.9%) contamination rate. Hazelnut was found in 15/113 (13.3%) snack items (Box 1), all of which had PAL (12 confectionery items, one cheesecake and two chocolate spreads). No peanut or hazelnut contamination was detected in non-snack items with PAL or in products without PAL. The avail-

Box 1. Examples of 'snack'¹ items which have been reported to have a higher risk of allergen cross-contamination

- Chocolates and chocolate-based foods, for example chocolate spreads
- Cookies/Biscuits
- Muesli bars/Cereal bars/'Trail' bars/Dried fruit bars/Nutrition bars
- Nut mixes
- Baked goods/baking mixes (cakes, pastries, scones)
- 'Confectionery' (such as sweets and candies)
- Ice cream

There is anecdotal data suggesting the seeded ('specialty') breads may also have a high risk of allergen cross-contamination. We would suggest that these items should always be avoided by nut-allergic individuals.

¹We acknowledge that 'snack' foods might be defined differently by different consumers and in diverse countries.

able data on frequency of peanut detection in foods with PAL (but where peanut is not listed as an ingredient) are summarised in Fig. 1. Whereas the risk of peanut contamination in snack foods (Box 1) ranged from 0.9–32.4% in eight studies [91–93, 95–99], the risk of peanut contamination in non-snack foods (predominantly frozen desserts, 'cold' (breakfast) cereals, pasta, sauces/powdered gravies and pre-packed quick/ready

meals) was 0% [92, 93, 96, 99] in four studies. Such analytical surveys are limited by the sampling strategy used (only 1–3 batches per food product are tested, which may miss batch-to-batch variation and especially particulate rather than homogenous contamination, where potential allergen is present in the food product but not in the sample analysed for contamination); nonetheless, there is a degree of consistency in the data.

Consumers desire clear labelling of foods products with possible allergen contamination, so that they can make an informed decision about the level of risk they are prepared to take [100]. Many appear to assume that the nature of the PAL statement conveys useful information on the magnitude of the allergen risk; for example, it is often assumed that an item with a 'may contain' label will only contain clinically negligible quantities of the allergen in question [32]. A survey of UK-based parents with a nut-allergic child found that 60% avoided products labelled 'may contain traces', but only 40% when phrased as 'made in a factory that uses nuts' – the assumption being that the latter conveyed a lower risk of contamination [101]. A similar observation has been reported in Australia [102]. However, the use of PAL is voluntary and the wording of such statements is not prescribed. Biochemical analysis of foods has highlighted that items with PAL which might be interpreted as conveying a lower risk (e.g. 'made in an environment...') frequently have levels of contamination of a magnitude similar to those labelled 'may contain...' [91, 99]. Indeed, one study from USA found that the rate of contamination was higher when the PAL stated 'prepared in a shared facility' than when the label read

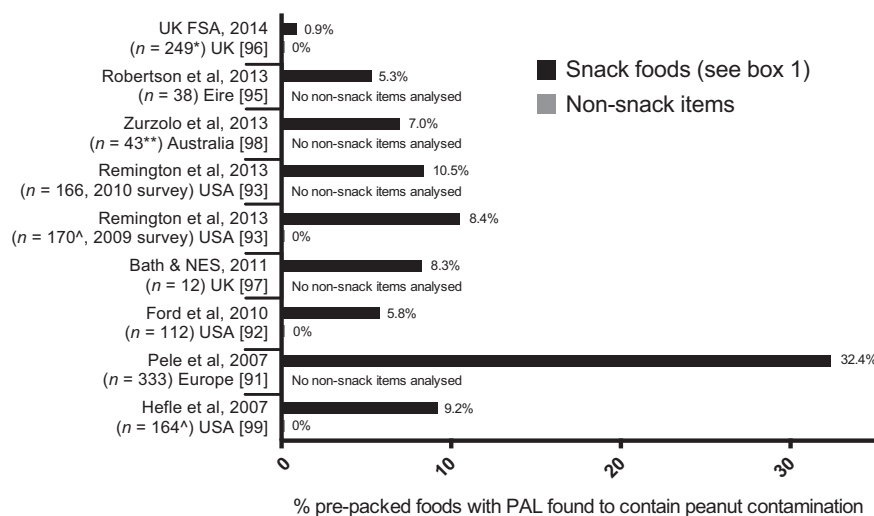


Fig. 1. Summary of studies reporting proportion of pre-packed foods with PAL to peanut which actually contain peanut on biochemical analysis. In all these studies, contamination has only been detected in 'snack' foods (as defined in Box 1). *508 items were assessed in the FSA survey, of which 249 had PAL to peanut. **Zurzolo *et al.* assessed 127 samples taken from 43 food products. ^Baking ingredients have been excluded in our analysis as these included ingredients such as mechanically grounded tree nuts which are clearly at high risk of peanut contamination. We have been unable to include the FSAI 2011 survey [94] due to absence of raw data.

'may contain (pea)nut' or 'produced on "shared equipment" with (pea)nut' [99]. Patients and their families should therefore be advised that the type of PAL has no bearing on the extent of the risk of contamination.

What level of peanut contamination is clinically significant?

The decision as to whether peanut-allergic individuals may eat foods with PAL to nuts, or whether they may consume other tree nuts and seeds, relies not just on the likelihood of contamination, but also whether the degree of contamination is sufficient to provoke an allergic reaction. A number of studies have attempted to apply scientific rigour to this; using statistical modelling, individual challenge data from large studies of DBPCFC in allergic individuals can then be used to derive a population threshold, often expressed as an ED10 level (the allergen dose needed to cause symptoms in 10% of the allergic population). Reported ED10 levels for peanut vary from 12.3 mg [42] to 133.8 mg [43], (the latter value may be artificially increased due to a relatively high initial dose of peanut used for some DBPCFC). However, thresholds are thought to vary widely within the same individual due to a host of poorly understood factors [103]. In addition, the higher the fat content of the matrix used for DBPCFC, the less likely patients are to experience the first 'warning' signs of an allergic reaction (oropharyngeal itch); thus, they may have an apparent higher threshold level of reactivity [104].

Population thresholds are helpful as a means to guide the use of PAL, the aim being to reduce the risk of harm from cross-contamination to a level considered tolerable, rather than eliminate risk altogether [105]. Some countries have attempted to use population thresholds to determine thresholds above which PAL should be used, for example, the VITAL (Voluntary Incidental Trace Allergen Labelling) scheme introduced in Australia and New Zealand [106]. We recently summarised the existing data from Europe and USA for allergen contamination in foods with PAL using VITAL cut-offs and found that up to 23% of snack items (including chocolates and cereal/muesli bars) contained sufficient peanut to trigger a reaction in allergic individuals [11]. Significant peanut contamination was not detected in other categories of foods (e.g. breakfast cereals, frozen desserts, pasta). One might therefore argue that on the basis of existing data, foods with PAL other than snack items that do not list nut as an ingredient are unlikely to trigger a reaction in a nut-allergic individual. However, the use of population thresholds for PAL has not been adopted elsewhere, primarily due to concerns as to variations in threshold (which can be several orders of magnitude) seen both between allergic individuals but also within the same individual

challenged on separate occasions [11, 103]. Studies are ongoing to evaluate the effect of external factors such as stress or sleep deprivation which might affect thresholds (<http://www.tracestudy.com>), given that this has been reported in patients undergoing oral immunotherapy to peanut [107].

Does the consumption of foods with PAL cause clinical reactions?

It is clear that many nut-allergic individuals do not heed PAL: Noimark *et al.* reported that over 50% of parents of nut-allergic children ignored PAL [101], a finding confirmed elsewhere [102]. The reasons for this include a belief by allergic consumers that such labelling is not credible due to the widespread use of PAL, particularly when PAL to nuts is seen to appear inappropriately, for example on a packet of peanuts [108]. Allergic patients may interpret their tolerance to foods with PAL as an indication of the mild nature of their allergy and thus put themselves at risk of a severe allergic reaction. Few studies have attempted to systematically investigate causes of accidental reactions in allergic individuals. Sheth *et al.* described 651 food-allergic patients on a Canadian registry who experienced an allergic reaction due to inadvertent allergen exposure and reported on the patients' opinions as to the cause of their reaction. In 37%, the allergic reactions were attributed to failure to read or heed PAL. 30% of reactions were attributed to the allergen not being clearly declared on the label (e.g. the allergen listed was not clearly visible, not described in plain language or there was an error in translation) while 35% of reactions were attributed to the absence of PAL in the presence of presumed cross-contamination [31]. However, given the fact that pre-packed foods with PAL are frequently consumed by nut-allergic individuals, there are remarkably few reports of significant allergic reactions to pre-packed foods due to nut cross-contamination. Indeed, the vast majority of inadvertent food reactions due to cross-contamination are thought to occur with non-pre-packed foods from catering outlets [11]. This is not surprising, given the difficulty many catering outlets have in providing meals suitable for consumption by nut-allergic individuals [109]. We are aware of two reports in the USA where consumption of foods with a PAL is thought to have caused a fatal reaction; one was over 10 years ago following consumption of cake, the other was more recent in a peanut-allergic teenager who consumed a snack bar (of dried fruits, nuts and seeds) which did not contain peanut as an intentional ingredient but did have a PAL to peanut (S. Taylor, personal communication). Within the UK, the fatal anaphylaxis register [110] does not have any records of fatalities due to proven cross-contamina-

tion of a pre-packed food with PAL (data from Richard Pumphrey). Furthermore, despite the regular consumption of pre-packed foods with PAL in many countries, a recent meta-analysis estimated that the rate of fatal food-induced anaphylaxis in peanut-allergic individuals is less than five events per million person-years [40].

Health professionals need to take into consideration a host of factors when making a risk assessment in order to provide appropriate advice with regard to PAL. A recent web-based survey of 239 health professionals (doctors including paediatricians, allergy specialists, GPs, nurses and dietitians) found that only 38% would advise peanut-allergic patients that avoidance of all foods with PAL was necessary. Factors resulting in more stringent avoidance being recommended included the presence of asthma, prior anaphylaxis to the food in question and prior mild reaction to a tiny amount. Of note, availability of an adrenaline auto-injector device (AAI) was not considered to be an important factor in the advice provided [111]. There is no literature relating to the scenario where a peanut-allergic individual is able to tolerate other nuts. For example, where a food is labelled 'may contain hazelnut', does this imply that such a food safe for a peanut allergic but hazelnut-tolerant individual? Given that such individuals may be less likely to read PAL or ingredient lists [112], any advice to introduce specific tree nuts must be given in the context of an individualised risk assessment with the patient. In such circumstances, availability of an AAI may be even more important.

Recommendations

As with every clinical decision, the use of evidence-based information and involvement of the patient is crucial. Current research to improve the utility of food labelling will hopefully facilitate decisions as to appropriate avoidance strategies for peanut-allergic individuals, reducing the impact of dietary avoidance on quality of life without increasing the risk of further allergic reactions. In each case, the balance between the allergic individual's nutritional requirements, quality of life and risk needs to be carefully assessed. Appropriate dietary advice is crucial for the child and family; in cases of multiple food allergies, in particular in young children, this should ideally be from a specialist paediatric dietitian to ensure nutritional adequacy. Furthermore, dietetic advice within the context of a multidisciplinary allergy clinic has been demonstrated to reduce the risk of accidental reactions [113]. The majority of fatal allergic reactions to nuts occur outside the home environment, and on this basis, we would recommend additional caution when eating unfamiliar foods in an unfamiliar environment, irrespective of the presence or absence of PAL. Allergic individuals might also be best

advised to follow more stringent dietary avoidance in circumstances where medical intervention for potential allergic reactions might be delayed due to non-availability of rescue medication and/or remote geographical location. International travel presents considerable challenges for the allergic individual because allergen awareness remains low in many countries. Street foods (prominent in many countries) are virtually uncontrolled with respect to allergens.

We have summarised the current available data from the UK, EU and USA on the risk of peanut cross-contamination in pre-packed snack vs. non-snack foods with PAL. Non-snack foods had a very low risk of peanut contamination (Fig. 1). It is clear that many allergic individuals already ignore PAL on pre-packed foods [101, 102] and do not appear to experience reactions as a consequence. For many peanut-allergic patients, particularly those who already consume foods with PAL to peanut, it is reasonable for them to continue to do so where the pre-packed item concerned is not a snack item (as defined in Box 1) or specialty bread product, when the allergic individual is clinically well and they are in an environment where rescue medication and a person qualified to administer this is readily available; in these circumstances, we propose that the risk of possible reaction is outweighed by benefits on quality of life. There remains a possibility of peanut contamination in non-snack foods (for example, by particulate contamination); thus, this advice may not be suitable for peanut-allergic individuals at higher risk of severe allergic reactions, or those with previous allergic reactions to minimal levels of peanut exposure. Therefore, advice regarding PALs must be tailored to the allergic individual and their family after discussion with their specialist: their comprehension of the issues involved, and their ability to recognise and appropriately manage any symptoms of a food-allergic reaction. This assessment is specific to peanut, and not to other allergens such as cow's milk, where cross-contamination presents a real risk to the cow's milk-allergic individual [11]. Finally, it is important to distinguish between pre-packed food products, and those sold loose from shops and catering outlets where it is thought the risk of cross-contamination is greater. Of note, the changes in legislation (implemented in December 2014) extend only to mandatory disclosure of allergens in non-pre-packed foods; the use of PAL will continue to be unregulated.

In our experience, and in other centres evaluating this approach [22], patients who are allergic to peanut or tree nuts may find it helpful to be able to eat other 'nuts' (peanut or other tree nuts) to which they are not allergic. This is particularly relevant where that nut is regularly consumed by the allergic individual's family on a regular basis, perhaps for cultural reasons.

Table 2. Arguments for and against the introduction of tree nuts in children with peanut allergy and vice versa

For	Against
Nutritional benefit of nuts	Misidentification of nuts
Quality of life: Cultural and social factors	Possible increase in anxiety
Decreased risk taking behaviour	Increased risk taking behaviour
Contamination of 'safe' (tolerated) nuts can be avoided, where the nuts are consumed directly from the shell	Accidental exposure to the index nut
Possible development of cross-tolerance to the index nut	Possible risk of subsequent development of allergy to the tolerated nut
Potentially halt the progression of peanut and/or tree nut allergies	Increased demand for hospital-based supervised introduction with resource implications

Introduction of specific tolerated nuts in the nut-allergic patient needs careful consideration based on demonstration of tolerance to the nut to be introduced; this may require a supervised introduction in hospital and has important resource implications. An important consideration is to ensure that any tolerated nut is not contaminated with a nut that the child remains allergic to. Contamination of tree nuts with peanut (and vice versa) is more likely to occur in factories where the same equipment is used to process and sort peanut and tree nuts. Thus, nuts within their shell are likely to have the lowest risk of contamination and are an appropriate option in the above circumstances. Education as to the identification of nuts is important, as both children and adults alike are unreliable at visually identifying tree nuts although most can correctly identify peanut [114]. The arguments for and against the introduction of tree nuts in children with peanut allergy and vice versa are listed in Table 2. Further research is needed to assess whether regular consumption of selective nuts (to which the affected individual is not allergic) increases the risk of accidental allergic reactions vs. the potential benefits on the child and family's quality of life.

Conclusions

- 1 It is possible to identify factors which are associated with increased severity of allergic reactions to peanut but not factors associated with a reduced severity of allergic reactions to peanut.
- 2 Food labelling:
 - (a) The precise wording used in PAL has no bearing on the risk of peanut or tree-nut contamination

(b) There are limited data on peanut/tree-nut contamination in food without PAL, although the recent UK FSA data address this concern. Further studies are needed to determine whether foods with PAL indicate a higher risk of peanut contamination than foods without PAL.

(c) The current PAL scheme is not currently working. Food manufacturers require clear guidance on threshold levels for peanut and tree nut-allergic reactions, so that this can be used in PAL, as has been applied for 'gluten free' labelling in coeliac disease. The VITAL scheme is a promising approach which should be adopted in future studies in foods with and without PAL and in snack (Box 1) vs. non-snack foods.

- 3 In some peanut-allergic patients, consideration should be given to allow the consumption of non-snack foods containing PAL following discussion with the patient's specialist (see earlier text for important considerations).
- 4 Consideration should be given to families who wish to introduce specific nuts into the diet to which they are not allergic, especially where this will prove beneficial for ethnic-specific diet, and with dietary advice to prevent cross-contamination with other nuts.
- 5 Finally, a randomised controlled trial is required to determine whether regular introduction of selective nuts to which the child is not allergic prevents the development of allergy to these nuts over time.

Conflict of interest

HAB, PJT, JOW and GL have received research support from the Department of Health through the NIHR comprehensive Biomedical Research Centre awards: to Guy's & St. Thomas' NHS Foundation Trust in partnership with King's College London (HAB, GL) and to Imperial College London Healthcare NHS Trust (PJT, JOW). PJT is in receipt of a Clinician Scientist award funded by the UK Medical Research Council (Award no. MR/K010468/1) and is a member of the Health Advisory Board for Allergy UK. ATF is Trustee of Allergy UK & Chair of its Health Advisory Board, as well as a member of the Anaphylaxis Campaign Scientific Advisory Board. SLT has received grants from multiple food companies (70 in total); this paper includes studies published by the Food Allergy Research & Resource Program, an industry-funded consortium, although the food companies do not control the design or results of the studies. JOW is supported by a NIHR Senior Investigator Award, has received research funding from the UK Food Standards Agency and is a trustee of the Anaphylaxis Campaign. GL is on the DBV Technologies sci-

entific advisory board, has received consultancy fees from the Anaphylaxis Campaign and National Peanut Board, has received lecture fees from Sodilac, Novartis, Nestlé Nutrition, GlaxoSmithKline and the Serono Sym-

posia International Foundation, and has stock/options in DBV Technologies. The rest of the authors declare that they have no relevant conflicts of interest.

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