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FOOD ALLERGY (D ATKINS, SECTION EDITOR)

Hidden Allergens in Foods and Implications for Labelling and Clinical Care of Food Allergic Patients

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Abstract The prevalence of precautionary labelling remains high. This prevalence restricts food choices, in some cases perhaps unnecessarily, for food allergic consumers. During processing, cross-contamination does often occur in food products due to the way that modern processing facilities operate; however, zero risk of cross contamination is not a realistic expectation. There is evidence to suggest that threshold levels below which reactions are not provoked in allergic individuals do exist and these have been established in the literature for peanuts. Additional information such as understanding threshold levels will be important to this field of research. The data that will be obtained from future clinical trials will help to underpin action plans for precautionary labelling. This paper will review the current literature that is available regarding: consumer behaviour and attitudes regarding precautionary labelling; risk to the consumer and analytical results of products that bear advisory labelling; the current debate regarding whether a tolerable level of risk can be obtained in food allergy; and finally, the newly introduced Voluntary Incidental Trace Allergen Labelling (VITAL) system operating in Australia.

Keywords Food allergy · Threshold · Allergens · Hidden · Precautionary labelling · Voluntary Incidental Trace Allergen Labelling (VITAL) · Eliciting dose (ED) · Risk · One dose clinical trial · Food allergic

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Introduction

Food allergy affects an estimated 6 % to 8 % of infants and young children and 3.5 % to 4 % of adults in the USA [1]. In Australia, the prevalence of challenge proven food allergy to either peanuts, raw egg or sesame in 12 month old infants has been estimated to be as high as 10.4 % (95 % CI, 9.3–11.5) [2, 3].

The primary approach for the management of food allergy is specific avoidance diets. Thus, consumers with food allergy rely on accurate information from product labels to help them choose products that are safe for consumption. However, products that contain precautionary labelling such as "may contain" can be misleading and confusing to consumers with food allergy. In addition, Helfe et al. (2007) found that an increasing number of consumers with food allergy were ignoring advisory labelling advice, possibly due to an increase in their usage such that consumers may develop familiarity and complacency regardless of whether the labels are conveying relevant information [1].

In this review we explain the current literature regarding precautionary labelling; consumer behaviour and attitudes regarding this type of labelling; risk to the consumer and analytical results of products that bear advisory labelling; the current debate regarding whether a tolerable level of risk can be obtained in food allergy and the newly introduced Voluntary Incidental Trace Allergen Labelling (VITAL) system in Australia.

Statutory Labelling Requirements

In most countries labelling information is covered by legislation that sets out guidelines regarding the type of information that must be provided to consumers. In 2003, food labelling legislation was introduced in Australia and New Zealand followed by similar legislation introduced by the European Commission and the U.S. Congress in 2003–2004 [4–6]. Current Australian legislation requires mandatory labelling of the most common allergenic foods: peanuts, tree nuts, milk, eggs, sesame, fish, crustaceans, soy and gluten as well as ingredients derived from those foods. Other nations have similar legislation in place for these allergens [4].

Voluntary Labelling

Despite the best efforts of manufacturers, hidden allergens can occur in foods via cross-contamination due to modern processing methods, therefore manufacturers have introduced precautionary labelling such as "May contain" or "Manufactured on shared equipment" to alert the consumer to the possible presence of hidden allergens [7]. At the point of consumption food products may have become cross-contaminated with residues of allergens due to shared farming practices, harvesting equipment, storage facilities, shared transportation vehicles, shared processing facilities and shared processing equipment [16]. This cross-contamination can leave a food allergic patient vulnerable to any of the symptoms that can occur in a patient upon exposure to hidden allergens, ranging from hives to life-threatening anaphylaxis.

The prevalence of precautionary statements on packaged goods has been reported to be high in Australia, Europe and the US. In our previous study we investigated the proportion of products with any precautionary labelling in an Australian supermarket and found that, overall, 65 % of products contained one or more precautionary statements to any of the nine most common allergens investigated (peanuts, tree nuts, egg, milk, sesame, crustaceans, fish, wheat and soy) [8]. The prevalence of labelling for peanut, tree nuts and egg in our current study was similar to the prevalence observed in the study by Koplin et al. (2010) three years ago, however, a possible methodological limitation common to both studies was the selection of a single supermarket for this assessment [9]. In comparison, in a study from 10 European countries of over 300 biscuits, the overall prevalence of precautionary allergen labelling for peanuts, hazelnut or nuts was 50 % [10]. In Australia this prevalence of precautionary labelling for peanuts and tree nuts was 78 % [8]. The largest study to date is by Pieretti et al. (2009) in which 20,241 products from 99 different supermarkets were investigated for advisory labels. Overall 17 % of products contained precautionary statements with the highest use of precautionary labelling identified in chocolate candy at 54 % and the most common allergens listed in precautionary statements were tree nuts at 61 % [11].

Consumer Attitudes and Behaviour Towards Precautionary Labelling

Consumers with food allergy are often advised to avoid products with precautionary statements even though the exact risks are unknown and the high rate of unregulated use reduces food choices for the allergic consumer [12]. General consumers balance a number of considerations when deciding what to eat, for example, the cost, taste and nutritional value [13], while food allergic consumers have the additional burden of avoiding allergens that may trigger a reaction.

A recent study sought to determine whether consumers with food allergy heeded precautionary statements [1]. In a 3 year period, a total of 1,270 consumers were recruited from patient conferences for food allergy. The authors found a 10 % decrease in that 3 year period in consumers heeding these statements. Behaviour also varied significantly according to the type of statement used. "May contain traces" was the most commonly heeded statement (86 % of allergic consumers avoided foods with this statement), followed by "manufactured on shared equipment" (79 %), and "manufactured in a facility that also processes…" (64 %).

The authors also analysed products that bore precautionary statements for the presence of peanuts. Surprisingly, the results showed that allergic patients were taking risks by disregarding some forms of advisory labelling because they were assuming incorrectly that statements such as "shared facility" and "may contain" indicate different levels of risk. In fact, detectable peanut residues were more common in products that had "shared facility" as a precautionary statement compared with those with a "may contain" statement [1]. Furthermore, Noimark et al. (2009) investigated the attitudes of parents of nut allergic children regarding precautionary labelling. The authors reported that 50 % of parents in the study were risk-taking by either ignoring warning labels or

assuming that there was a different level of risk depending on the wording on the label [14].

In addition, a European study investigated whether current food labelling practices are perceived to be adequate by food-allergic consumers. The authors reported that food-allergic consumers are not satisfied with the current labelling practices, as the uncertainty of cross contamination leads to personal stress and feelings of insecurity [15].

The Risk to the Consumer and Analytical Results of Products that Bear Advisory Labelling

Cross-contamination is a common cause of accidental exposure of food allergic patients to an allergen [16]. As previously noted, Pele et al. (2007) compared the relationship between analytical results and precautionary labels in 315 cookies and 254 chocolates. Their investigation was widespread as they obtained food products from 10 European nations. The analysis was performed by using the enzyme-linked immunosorbent assay (ELISA). Of the 315 cookies analysed, 25 % contained traces of hazelnuts and 23 % traces of peanuts. Of the 254 chocolates analysed, 75 % of the products contained traces of hazelnuts and 37 % contained traces of peanuts.

In addition, the majority of food products did not declare the allergen of question in the main ingredient list; however, most contained a precautionary statement. This may be problematic, as consumers are left to decide whether to consume the product without any assurance that the product is safe [10].

Hefle et al. (2007) analysed 200 food products for the possible presence of peanut protein. The results show that peanuts were detected in 10 % of all products tested. Of products that bore a precautionary statement, detectable peanut protein ranged from 3–4000 ppm [1].

Furthermore, Crotty and Taylor (2010) determined the potential likelihood of milk exposure in milk allergic subjects who were consuming products with precautionary milk statements. A total of 100 food products were analysed. Detectable milk residues were found in 60.7 %. For products bearing precautionary labels, the milk concentrations ranged from 3.4–15,000 ppm [17].

Recently, Ford et al. (2010) performed 599 allergen assays on 401 food products for the detection of milk, egg and peanut proteins. Their aims were to determine the level of contamination for products with precautionary statements and for those without. Among those that contained precautionary statements, 5.3 % contained detectable residues of allergenic food (concentration range from 3–222 ppm) versus 1.9 % among products that bore no precautionary statement (concentration range from 17–124 ppm) [18].

The differences between the above mentioned studies may be attributable to differences in product and food category selection; however, the findings from these studies indicate a real risk for consumers and highlight how important it is to determine if a tolerable level of risk in food allergy can be achieved, as zero risk is not a realistic option.

Current Debate Regarding Whether a Tolerable Level of Risk Can Be Obtained in Food Allergy

There is growing concern among food allergy sufferers and the food industry about cross-contamination. The food industry is now making widespread use of precautionary labelling; however, this diminishes food choices, which has a negative influence on the quality of life of food allergy sufferers. There is evidence to suggest that threshold levels below which reactions are not provoked in allergic individuals do exist, suggesting that precautionary labelling may be unnecessary where trace contamination is below these thresholds [19]. Existing studies have focused on establishing threshold levels for peanut allergy, as peanut allergy is among the most prevalent and severe food allergies and the unintentional consumption of peanut by peanut allergic individuals is a leading cause of fatal food allergic reactions [20]. Low dose clinical challenge trials in individuals with peanut allergy have documented that the most sensitive individuals challenged thus far to low doses react only with mild, objective symptoms [19].

Taylor et al. (2009) explain that an individual's elicitation threshold lies between the no observed adverse effect level (NOAEL) which is the highest dose that will not cause any symptoms, and the lowest observed adverse effect level (LOAEL) which is the lowest dose capable of causing symptoms in the allergic consumer [21••]. The authors examined NOAEL and LOAEL in 286 patients with objective symptoms to double-blind placebo-controlled peanut challenges. The researchers were able to establish estimates of eliciting doses (ED) that cause objective allergic reactions in 10 % (ED_{10}) and 5 % (ED_5) of the population. The established ED5 with 95 % confidence intervals (CI) is 5.2 mg of peanut (expressed as whole peanut) [21••].

In the studies mentioned above, we highlighted the difficulty in guaranteeing that all food products are free from cross-contamination; however, it is important to note that in the studies mentioned above, observed levels of cross-contamination are lower than the predicted ED5 that has been demonstrated to cause a reaction in only 5 % of the population. Thus, we can assume that the majority of products that contain detectable levels of peanut would most likely be tolerated by a large proportion of the peanut allergic community.

One limitation of these studies is that the interpretation of the data used to obtain the eliciting doses is complicated by several factors including whether a reaction is occurring to a

discrete threshold dose of allergen or to the cumulative dose consumed to the point where the challenge is discontinued. As dosing schedules are usually every 15–20 minutes and reactions may occur up to 1 hour after ingestion, a particular reaction might be related to any of the previous individual doses.

There may also be problems with the way in which peanut allergic subjects have been selected for existing studies. Strict inclusion and exclusion criteria exist for these challenges; therefore, participants may not be representative of all subjects who have peanut allergy.

Recently Madsen et al. (2011) conducted a workshop that brought together key representatives from the main stakeholders (regulators, industry, clinical researchers and patients) to discuss a tolerable level of risk with regard to allergic reactions to food. The discussion revealed two main outcomes [22••].

Outcome 1: The workshop defined action levels as a level of allergenic food that may result in a manufacturer taking action, such as labelling of food products as "free from", application of precautionary labelling or removal of the product from sale where necessary. The workshop suggested that action levels should be derived from the currently available data and that a tolerable level of risk should be proposed.

Outcome 2: The workshop agreed to a one-dose clinical trial in multiple centres across the world using a standardized food challenge protocol with a low allergen dose. The previously determined ED5 was proposed for use in the study, as this would assure patient safety and help to validate the ED5 and provide additional information about the type of reactions that might be expected at this level [22••]. The one-dose clinical trial is likely to benefit both consumers and the manufacturing industry by the provision of evidence regarding the frequency of reactions to a pre-defined, rather than extrapolated, threshold amount of peanut in food products. In addition, this would aid clinicians in educating the allergic individuals regarding precautionary labelling, as currently allergists vary their advice based on an informed judgement of who is at greatest risk for a severe adverse reaction.

Voluntary Incidental Trace Allergen Labelling (VITAL)

Voluntary Incidental Trace Allergen Labelling (VITAL), recently revised as VITAL 2.0 [23••] is currently the most scientific system of action levels to deal with possible cross-contamination. The VITAL procedure, which was developed in Australia by the Food Allergen Bureau (an industry funded body), encourages manufacturers to undergo a more intensive investigation into the possible presence of allergens in foods prior to their release to consumers. It also utilises a new and unique precautionary statement: "May be Present". The benefits of this risk assessment tool are that it allows the examination of possible sources of allergen cross-contamination from raw material and the processing environment. In addition, it also allows evaluation of the possible amount of cross-contamination using an interactive action level grid. The VITAL grid incorporates a two-fold action grid: if the level of cross-contamination is equal to or above the action level then VITAL's "may be present" statement is used as a precautionary statement to replace all other precautionary statements; if it is below the action level concentration then no precautionary labelling is required.

The VITAL grid, initially developed in Australia, has attracted international interest and certain international manufacturers have now implemented the use of this risk assessment tool. However, a limitation of the VITAL process is that there is no material on products that alerts the consumer that the products that bear the VITAL statement have been assessed by the VITAL process [23••]. In addition, we have previously reported that since its establishment in 2007, its use by manufacturers has been low [8].

Conclusions

Modern manufacturing processes present a risk of cross-contamination due to the use of shared facilities and equipment for processing of different foods. This presents a hazard to allergic consumers, resulting in the abundant use of precautionary labelling statements on processed goods, which restricts food choices and is difficult for allergic consumers to interpret. However, although cross-contamination of foods may lead to symptoms in food allergic individuals, these symptoms will only take place when the exposure exceeds the individual's threshold dose for reaction. Large collaborative studies such as the current one dose clinical trial taking place in multiple centres across the world will help to provide further information about the ability of allergic individuals to tolerate a predefined low dose of allergen. The data obtained from these trials can then be incorporated into the VITAL process which will aid manufacturers and consumers alike.

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