

Food Allergy and the Food Industry

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Current Allergy and Asthma Reports 2004, 4:55–59

Current Science Inc. ISSN 1529-7322

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Although most food-allergic reactions occur after ingestion of nonpackaged food products, the food industry has been subjected to increasing scrutiny of their allergen controls; the resulting impact on the industry has been remarkable.

Undeclared food allergens have been responsible for many food product recalls during the past 13 years, and the food industry has made significant investment, effort, and improvements in allergen control during this time. Recently, tests for some allergenic foods have been commercialized, and proven useful to the industry in controlling allergens and helpful for regulatory agencies investigating food-allergic consumer complaints. However, testing methods still do not exist for some of the common allergenic foods. Labeling initiatives have been pursued to make ingredient listings more easily understood by food-allergic consumers, but further improvements could still be made. Additional research to determine eliciting doses for allergenic foods is needed to enable science-based risk assessment and risk management.

Introduction

It is estimated that there are 29,000 emergency room visits and approximately 150 deaths in the United States each year due to anaphylactic reactions to foods [1••]. Eight foods or food groups are responsible for 90% of the allergic reactions to foods: peanuts, tree nuts, milk, eggs, fish, crustacean shellfish, soybeans, and wheat [2]. Individuals with food allergies can react adversely to the ingestion of very low amounts of allergenic foods from unexpected sources, including trace residues that contaminate other foods. Most reported inadvertent food-allergic reactions do not occur to packaged food products, but because packaged food products have ingredient declarations regulated by federal agencies, the food processing industry has been subjected to increasing scrutiny of their allergen control programs. Food processing equipment was historically never designed for removal of allergen residues, and the food industry has had to actually change the way food is manufactured in some cases to address allergen control. Corporate allergen control strategies address each aspect of the manufacturing process [3,4].

Allergen Control Strategies in the Food Industry

The food industry often uses shared equipment and facilities for the production of processed foods with a variety of different formulations. The proper management of the use of such shared equipment is essential to prevent cross-contact that could allow potentially hazardous residues of an allergenic food into another product. Several strategies exist for the use of shared equipment and shared facilities. Dedicating one or a few lines to the manufacture of a certain allergenic food is one such strategy. For example, all peanut-containing formulations could be made on one dedicated line. In certain types of food manufacture, the use of dedicated lines or equipment can be more complicated. Many companies have numerous processing lines and many products, so dedicating lines is not an option.

When a processor cannot dedicate a line, there are other approaches used to ensure that products are not contaminated with allergen residues. Scheduling of manufacture is a powerful technique in this regard; this is done by grouping of allergenic foods, such as manufacturing all dairy-containing foods together, egg-containing foods together, and so on. In addition, whenever shared equipment is used, effective clean-up must occur between manufacture of an allergenic formulation and manufacture of the next product. Clean-up strategies will vary with the nature of the products being manufactured and the design and composition of the processing equipment. Many companies go to the extent of using color-coding for sanitation tools, each color dedicated to a type of allergen. The greatest challenges are found with processing operations that must be cleaned without the use of water or detergents. In some types of food processing, such as chocolate processing or dry blending, wet washing of equipment would introduce other food-safety risks, such as microbial pathogens, and, therefore, cannot be used. Useful dry cleaning techniques include vacuuming and hand-wiping of equipment. How clean is clean enough? That question is hard to answer. At minimum, all visible residues of the allergenic product must be removed. Although this sounds simple, verification of "visibly clean" can be lengthy, involving disassembly of certain pieces of equipment. In some manufacturing operations, such as the use of long baking ovens, the assessment of "visibly clean" can be extremely difficult.

In addition, the food industry has incorporated allergen controls into the new product development stage. This strategy has changed the culture and process that product developers go through in designing new food products. If a new

product contains allergenic ingredients, it has to be dealt with differently than if no allergenic foods are contained in the formulation. In the United States, peanut-containing products are very popular, but some companies have made the decision to forego a new peanut-containing product to avoid handling that product through the manufacturing process, including appropriate allergen controls and sanitation procedures. Although it is not possible to make all new food products without the major food allergens, if product developers can keep from using some commonly allergenic foods in food products in the first place, there will be fewer issues of concern. Not only must a manufacturer have allergen-control programs in place in their plants, they must ensure that their raw materials suppliers do also. It is absolutely essential that complete information on raw materials is provided by raw materials suppliers. The processor has to obtain complete ingredient information on all raw materials so that allergen issues can be dealt with appropriately. Many companies have instituted allergen-auditing programs for their suppliers to make sure they have the best information available about what is in their raw ingredients.

Regulatory Actions

In the United States and other countries, recalls due to undeclared allergens have been increasing. In 1999, a total of 68 recall actions involving 236 food products were recalled by the United States Food and Drug Administration (FDA) for undeclared allergens [5••]. From fewer than 200 to as many as 100,000 food packages were affected per recall. The two most common problems leading to recalls were ingredient statement omissions or errors and contamination caused by shared equipment, but 18% of the recalls were due to supplier or employee errors. Most recalls that year were discovered by consumers (50%), and in 34 cases, allergic reactions to the offending food were reported. Of these 34 reactions, 24 (71%) described their reactions as mild, whereas the remaining 10 (29%) indicated more severe allergic reactions. Other parties besides consumers who played a role in identifying products that were recalled included the FDA, state regulatory agencies, the food industry, and the Canadian Food Inspection Agency. The FDA authors of this study indicated that the increase in regulatory recalls for undeclared allergens might have been due to an increased ability to detect allergens and not necessarily because of a true increase in the presence of undeclared allergens in food products.

Emerging Issues in Allergen Control

Besides those discussed earlier, key issues in food allergen control today are the allergenicity of certain ingredients, the use of test kits for allergen residue detection, the minimum amount of allergenic foods that can elicit a reaction in a sensitive individual, and appropriate labeling for allergens.

Allergen-derived Ingredients

The use of ingredients derived from commonly allergenic foods, such as edible oils, lecithins, gelatins, and others, should be balanced with allergen control. If one introduces a truly allergenic component into a food, the control strategies listed earlier must be employed. However, many ingredients derived from allergens have little or no protein in them, and the allergens might not be present in the ingredient. In some cases, as for highly refined oils, clinical, double-blind, oral challenges have proved that these substances are safe for ingestion by food-allergic individuals. For other allergen-derived ingredients, not enough information has been obtained yet or clinical studies have not been done. The food industry must balance the use of certain allergenic ingredients while allowing food-allergic consumers to have the widest variety of foods from which to choose; often, these decisions cannot be easily made, because the necessary clinical research has not been done. For example, many soy-allergic individuals do not avoid soy lecithin, a common food ingredient, and the levels of protein in soy lecithin are apparently low enough not to induce allergic reactions. Therefore, the food industry can likely use this ingredient without much concern over soy-allergen issues. Many allergen-derived ingredients are currently being examined for their allergenicity, and there will be much more information in this area gained in the next few years.

Detection Methods

Until approximately 6 years ago, no commercial methods for the detection of allergenic residues in foods or processing equipment were available. Before that time, and to a certain extent now, food companies had to rely on their allergen controls and good manufacturing practices to avoid the presence of undeclared allergens in packaged food products. The methodology for detection of allergenic residues in foods is improving with the advent of enzyme-linked immunosorbent assays (ELISA) for allergenic foods. These tests are most useful for application in the food industry, in ensuring that raw ingredients, processing equipment, and products are free of undeclared allergenic residues.

Although some commercial methods are available, there are no reliable methods available at the present time for some of the common allergenic foods. As new methods are developed and commercialized, the food industry is increasingly monitoring food products produced on shared equipment or in shared facilities for the presence of residues of allergenic foods. Commercial ELISAs are available for the detection of peanuts, egg, milk, almond, whey, sesame seeds, and wheat gluten. These current immunoassays can detect residual levels of allergenic foods at a sensitivity level of about 1 to 2.5 ppm (mg allergenic food per kg product). In addition, there are methods developed that have not yet been commercialized. In addition to those listed above, methods for hazelnut [6,7]

and walnut have been reported [8]. However, there is a need for more of these types of assays, as we lack these important tools for some of the most commonly allergic foods (*eg*, crustaceans, fish, and soybean). In addition, although many of these methods are used by the industry, most of them have not been validated in extensive interlaboratory studies.

In some situations, sensitive and specific immunoassays are available for the assessment of the effectiveness of clean-up. In some types of food manufacture, contaminated product might appear episodically for hours after changeover. This episodic, sporadic contamination can be due to equipment design, in that allergen-containing product can be hung up for long periods and then break loose at various times, contaminating subsequent product. To address this challenge, food companies design elaborate sampling plans. These immunochemical tools have allowed better risk assessment, thereby allowing greater protection of the food-allergic consumer, providing tools for the allergist to investigate cases of possible "hidden" allergens in foods, and allowed regulatory agencies to better investigate food-allergic consumer complaints. In addition, they can provide the information needed for more complete and accurate labeling of food.

In some studies using these detection methods, several packaged food products were found to contain undeclared tree-nut residues at levels that could be potentially hazardous to allergic individuals [6,7,9,10•]. For egg, 22 egg-free retail pasta samples were found to be contaminated [11]. In another study, 13 products yielded no detectable egg residues [12]. In another report, a commercial peanut kit was used to show that chocolate bars were contaminated with peanut [13•]. Often, residues exist in retail food products, with no report of reactions. This could be because either the eliciting levels of the allergen residues in the products are below the minimal doses for that particular allergenic food or because food-allergic individuals do not buy certain products that they feel are vulnerable to contamination with undeclared allergenic food residues.

Eliciting Doses

Very little information exists upon which to estimate the minimal eliciting dose for specific allergenic foods. Anecdotal reports indicate that reactions have occurred from such incidental contact as opening packages of the offending food, wiping counters or tables containing unseen residues, inhaling vapors from cooking food, use of shared utensils, and kissing someone who has eaten the offending food [14]. However, a recent report has shown that the mere presence of peanut butter in a room, a concern for many peanut-allergic individuals, does not elicit allergic reactions in sensitive individuals [15••].

Although such reports confirm that ingestion of very small amounts of allergenic foods might provoke allergic reactions in some exquisitely sensitive individuals, they do not provide quantitative information about the lowest pro-

voking doses. The ability to detect residual levels of allergenic foods must preferably be coupled with information on doses that elicit allergic reactions to provide the required level of protection for food-allergic consumers. Good manufacturing practices in the food industry and regulatory limits imposed by governmental agencies should be based on knowledge of minimal elicitation levels. The dose needed to provoke an allergic reaction is not precisely known and is likely to vary from one allergic individual to another [16••]. Although complete avoidance of allergenic foods is advocated for food-allergic individuals, evidence indicates that they can tolerate very small quantities of the foods in their diets without experiencing allergic reactions [16••].

One way to estimate the lowest eliciting dose of food is from actual samples from allergic consumer complaints. Relatively few reports of adverse reactions to documented residues of allergenic food exist in the literature. This is likely due to several factors: a lack of simple methods for the analysis of the implicated food product for residues of commonly allergenic foods, uncertainty about the amount of food eaten, and questions about the circumstances surrounding the inadvertent ingestion, such as possible other sources of the offending food. For example, in a case report by our group, together with colleagues at the Mayo Clinic several years ago [17], a milk-allergic child apparently reacted after eating approximately 4 to 6 oz. of sorbet containing fewer than 200 µg of whey protein. However, upon questioning, it was discovered that some members of the family were enjoying ice cream at the time of the incident. Although there are some data available in the literature on allergic reactions and fatalities from foods contaminated with allergens, uncertainty exists relative to the reported levels of these residues because many of the analytical methods used have not been fully validated. Although such episodes reveal the hazards posed by undeclared residues of allergenic foods contaminating other foods, they are not particularly suitable for establishing the lowest provoking dose.

The lowest eliciting dose might best be defined as the lowest amount of the offending food that would elicit mild, objective symptoms (*eg*, mild urticaria, oral allergy syndrome) in the most sensitive individuals. We have moved away from the concept of challenging with food in capsules, preferring the use of food vehicles, which mimics more closely real-life experiences and lets the physician observe reactions initiated in the oral cavity, thereby stopping challenges at an earlier stage before more severe symptoms begin. Large patient-to-patient variations have been observed in low-dose challenge studies to date. The lowest provoking dose levels are an important part of risk assessment for the food industry, but, in addition, determination of minimal eliciting doses provides more accurate information to the food-allergic consumer as to their possible sensitivity level. Sufficient results are available in the medical literature to conclude that the eliciting doses for commonly allergenic foods are finite and measurable. However, elicitation doses for different aller-

genic foods—for example, peanuts and eggs—might not necessarily be equal, and more research is needed for better risk assessment. Standardization of various aspects of threshold-dose studies is needed so that data can be compared and amassed in a logical way. It is anticipated that many more threshold-dose studies will be performed in the near future.

Labeling

The only line of defense that a food-allergic consumer has against a reaction is the ingredient listing on packaged food products. Food-allergic consumers must educate themselves about label designations and ingredient names and always perform diligent reading of labels. In food-service situations, labels are not available, and, therefore, it should not be surprising that many of the most severe food-allergic reactions occur in food-service settings. However, with packaged foods products, the ingredient listing assumes overriding importance in the protection of food-allergic consumers. In a recent study, parents of food-allergic children were asked to look at a variety of food labels and indicate whether or not the food was safe for this child to eat. Peanut products were identified correctly by the parents in 54% of cases, but only 7% correctly identified milk and only 22% correctly identified soy. Wheat and egg were correctly identified most of the time. The authors concluded that with the current labeling practices in the United States, most parents are unable to identify common allergenic food ingredients, and they stressed that there was a need for improved labeling with plain terminology as well as diligent education of the affected individuals [18••].

Ingredient labeling regulations differ significantly from one country to another. Certain labeling practices still remain confusing, and there are initiatives or regulations in some countries now to make ingredient listings more easily understood or more complete. In the United States, a group called the Food Allergy Issues Alliance, comprising various food-industry trade associations, a food-allergic consumer group, and other interested parties, developed a set of guidelines for allergen labeling to make terms used on ingredient declarations more clear to food-allergic individuals [19]. The guidelines and related other materials can be found at <http://www.nfpa-food.org/science/AllergenLabelin.htm>.

Some countries also allow precautionary labeling such as “may contain peanuts” and/or similar statements. Precautionary labeling usually results from use of shared equipment. As noted earlier, in certain manufacturing situations, despite good manufacturing practices and allergen-control plans, there can still be residues of allergenic food that make their way into a food product that is not supposed to contain them. If the shared equipment cannot be adequately cleaned, use of precautionary labeling is prudent. However, the current regulatory situation relative to precautionary labeling varies widely around the world. This might confuse food-allergic

consumers as they travel or purchase imported packaged foods. In some countries, precautionary labeling is expressly allowed and is widely encountered on food products. In the United States, many different statements of this type appear on food labels including “may contain,” “manufactured on shared equipment with,” and “manufactured in the same facility as.” The diverse wording of statements in the United States has caused consumer confusion. Although precautionary labeling might be a good idea, its use should be strictly controlled. The food industry might choose to use this type of labeling more widely than would be necessary. In the United States, the regulatory authorities have indicated that precautionary labeling cannot be used as a substitute for good manufacturing practices. That means that if the processor can clean the shared equipment sufficiently, then precautionary labeling should not be used as a substitute for adequate cleaning. If precautionary labeling is used too widely, the food industry might incur criticism from food-allergic consumers. Precautionary labeling should only be used in circumstances in which contamination is documented, uncontrollable, sporadic, and potentially hazardous [20]. In addition, food-allergic consumers should always avoid products that are labeled with precautionary allergen statements, as the industry uses this type of labeling to communicate risk.

Conclusions

The packaged food industry has been working on controlling allergenic food residues for more than 15 years. Large-scale capital investment, changes in equipment design, and transformations in the way food is processed have been implemented to address concerns over undeclared residues in foods. Certain manufacturing situations provide challenges in allergen control, such as shared equipment, and precautionary allergen labeling (*eg*, “may contain peanut”) is sometimes used in these cases to alert the food-allergic consumer of the possible presence of residues. If precautionary labeling is used too widely by the food industry, criticism will likely arise from food-allergic consumers. Hence, precautionary labeling should only be used in circumstances in which contamination is documented, uncontrollable, sporadic, and potentially hazardous. Food-allergic consumers should always avoid products that are labeled with precautionary allergen statements, as the industry does use this type of labeling to communicate existent risk. Specific and sensitive commercial ELISA methods for some common allergenic foods are now being used by the food industry to monitor their processes, but more assays of this type are needed. In addition, much more research is needed on the minimum amount of allergenic foods that will provoke an allergic reaction, as this type of information is important for science-based risk assessment of allergen concerns by both the food industry and regulatory agencies.

References and Recommended Reading

Papers of particular interest, published recently, have been highlighted as:

- Of importance
- Of major importance

1. •• Bock SA, Munoz-Furlong A, Sampson HA: **Fatalities due to anaphylactic reactions to foods.** *J Allergy Clin Immunol* 2001, 107:191–193.

This paper describes a series of 32 fatal food anaphylaxis reactions and shows which foods were responsible. There are several interesting findings in this paper, such as most individuals had asthma, the lack of availability of epinephrine appeared to be a factor, and peanuts and tree nuts were responsible for more than 90% of the fatal reactions. This is the most comprehensive study of fatal food-induced anaphylactic reactions to date.

2. Food and Agriculture Organization of the United Nations: **Report of the FAO Technical Consultation on Food Allergies.** Rome, Italy. November 13–14. 1995.
3. Deibel K, Trautman T, deBoom T, *et al.*: **A comprehensive approach to reducing the risk of allergens in foods.** *J Food Prot* 1997, 60:426–441.
4. Huggett AC, Hischenhuber C: **Food manufacturing initiatives to protect the allergic consumer.** *Allergy* 1998, 53(Suppl 46):89–92.
5. •• Vierk K, Falci K, Wolyniak C, Klontz KC: **Recalls of foods containing undeclared allergens reported to the US Food and Drug Administration, fiscal year 1999.** *J Allergy Clin Immunol* 2002, 109:1022–1026.

In this paper, the US Food and Drug Administration food product recalls due to undeclared food allergens are summarized. Factors contributing to the recalls are discussed, and the circumstances under which many of the problems were discovered are indicated.

6. Holzhauser T, Vieths S: **Quantitative sandwich ELISA for determination of traces of hazelnut (*Corylus avellana*) protein in complex food matrixes.** *J Agric Food Chem* 1999, 47:4209–4218.
7. Koppelman SJ, Knulst AC, Koers WJ, *et al.*: **Comparison of different immunochemical methods for the detection and quantification of hazelnut proteins in food products.** *J Immunol Met* 1999, 229:107–120.
8. Niemann L, Hefle SL: **Validated ELISA for detection of undeclared walnut residues in food.** *J Allergy Clin Immunol* 2003, 111:S248.
9. Hlywka JJ, Hefle SL, Taylor SL: **A sandwich enzyme-linked immunosorbent assay for the detection of almonds in foods.** *J Food Prot* 2000, 63:252–257.

10. • Wensing M, Koppelman SJ, Penninks AH, *et al.*: **Hidden hazelnut is a threat to allergic patients.** *Allergy* 2001, 56:191–192.

This article describes the investigation of allergic reactions in a hazelnut-allergic patient that was eventually traced to a chocolate spread that was not supposed to contain hazelnut. Immunochemical analysis assisted in the identification of the unexpected source of reactions.

11. Hefle SL, Jeanniton E, Taylor SL: **Development of a sandwich enzyme-linked immunosorbent assay (ELISA) for the detection of egg residues in processed foods.** *J Food Prot* 2001, 64:1812–1816.
12. Yeung JM: **Determination of egg proteins in food products by enzyme immunoassay.** *J AOAC Int* 2000, 83:139–143.
13. • Vadas P, Perelman B: **Presence of undeclared peanut protein in chocolate bars purchased in the Toronto area.** *Can J Allergy Clin Immunol* 2001, 6:116–117.

This paper focuses on an investigation of six different chocolate products obtained from the retail marketplace in Canada and tested using a commercial peanut detection ELISA kit. The data show undeclared peanut in some products.

14. Hallett R, Haapanen LA, Teuber SS: **Food allergies and kissing.** *N Engl J Med* 2002, 346:1833–1834.
15. •• Simonte SJ, Ma S, Mofidi S, Sicherer SH: **Relevance of casual contact with peanut butter in children with peanut allergy.** *J Allergy Clin Immunol* 2003, 112:180–182.

This article indicates that allergic reactions are not elicited by merely the smell of peanut butter.

16. •• Taylor SL, Hefle SL, Bindslev-Jensen C, *et al.*: **Factors affecting the determination of threshold doses for allergenic foods: How much is too much?** *J Allergy Clin Immunol* 2002, 109:24–30.

The existing information in medical literature on minimum eliciting doses of allergenic foods is examined, and key issues in making risk-management decisions on the basis of such information are identified. A good description of most of the issues surrounding eliciting dose studies is provided, and some lowest provoking dose data are summarized from the literature.

17. Laoprasert N, Wallen ND, Jones RT, *et al.*: **Anaphylaxis in a milk-allergic child following ingestion of milk-contaminated lemon sorbet.** *J Food Prot* 1998, 61:1522–1524.
18. •• Joshi P, Mofidi S, Sicherer SH: **Interpretation of commercial food ingredient labels by parents of food-allergic children.** *J Allergy Clin Immunol* 2002, 109:1019–1021.

Given the current labeling regulations, many parents of food-allergic children cannot correctly identify some allergenic foods in ingredient listings.

19. Taylor SL, Hefle SL: **Food Allergy Issues Alliance and food allergen labeling guidelines.** *Food Allergy Intolerance* 2002, 3:37–42.
20. Taylor SL, Hefle SL: **Good manufacturing practices for allergenic foods: packaging and labeling strategies.** *Food Allergy Intolerance* 2001, 2:53–58.