

Trends in Food Allergy Research, Regulations and Patient Care

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This review provides an overview of food allergies, their impact on affected individuals and caregivers, regulatory activities, and current research efforts to improve allergen management and patient care. Food allergies have been reported to affect up to 32 million Americans, including approximately 6 million children. The Centers for Disease Control and Prevention reported that food allergies in children have clearly increased by 50% between 1997 and 2011. Recent years have seen significant advances in the understanding of responses to food allergens such as the development of response thresholds that hold promise for developing more informative labels on food packaging. Staying current on advances in food allergy research will allow healthcare and nutrition practitioners to provide evidence-based guidance to individuals they serve. *Nutr Today*. 2022;57(2):64–69

Although promising therapeutic treatments are being developed, there are no cures for food allergies. The most recognized food allergy from a public health standpoint has been an immunoglobulin E (IgE)-mediated hypersensitivity to food because this type of food allergy has the potential to cause acute life-threatening reactions including anaphylactic shock.¹ Immunoglobulin E is a class of antibodies that is normally found in very small amounts in the blood. A rise in IgE levels, especially when observed in combination with patient allergic history, is an indication of a hypersensitivity or a true allergic response. It should be noted that IgE is also involved in immune responses to parasitic infections and environmental allergens such as pollen and, thus, a rise in IgE is not a definitive diagnosis of a food allergy per se.

The immune system plays a central role in fighting off bacteria, viruses, and other organisms that can cause illness. However, if someone has a food allergy, his/her immune system treats the allergenic protein as a threat. Allergic patients produce IgE antibodies specific for foreign antigens. These antibodies bind to IgE-specific receptors on the surface of mucosal and cutaneous mast cells and circulating basophils. Allergens that are introduced by inhalation, ingestion, or cutaneous or intravenous exposures cross-link IgE bound to these effector cells, which results in aggregation of the receptors causing the immediate release of histamine and, shortly thereafter, the release of newly formed mediators such as arachidonic acid products and cytokines. This cascade of responses, including the cytokines, is responsible for immediate and late allergic responses.

United States law recognizes 9 major food allergens: milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, sesame, and soybean for specific labeling purposes. The addition of sesame is based upon a law recently enacted by Congress; labeling requirements enter into force in January 2022.²

Food intolerances are different from allergies; food intolerance refers to the inability to digest or absorb certain foods. For example, lactose-intolerant individuals do not have enough of the enzyme lactase to break down lactose in dairy products. Food intolerances are generally not life-threatening.

WHAT ARE FOOD ALLERGIES?

Food allergies occur when the body's immune system reacts to certain allergenic proteins in foods. Food allergies vary in severity from mild symptoms such as hives to severe and potentially life-threatening symptoms such as anaphylactic shock.

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WHAT IS THE IMPACT OF FOOD ALLERGIES ON SENSITIVE INDIVIDUALS?

Food allergies represent a serious public health issue with life-threatening consequences to those affected, especially children. In addition, food allergies are an economic burden on families with affected children³ who also experience reduced quality of life.⁴ It is estimated that approximately 32 million Americans (slightly under 10% of the US population) have food allergies, including close to 6 million children. In Canada, an estimated 7% of the population has at least 1 food allergy based on self-assessment surveys.⁵

More concerning, perhaps, is the trend of increasing prevalence of food allergies in all segments of the US population, notably children, although some of the increase may be due to better reporting over time. The prevalence of food allergies in children has increased 1% to 2% per decade according to one study.⁶ Recent data indicate that more than 40% of children with food allergies have experienced a severe allergic reaction such as anaphylactic shock.⁷

Peanuts rank among the top food allergens causing severe reactions among Americans.⁸ In sensitive peanut-allergic individuals, peanut protein consumption can lead to hives, shortness of breath, or nausea within minutes of exposure. For a subset of individuals, exposure to small amounts can result in anaphylactic shock.

In the absence of a cure for food allergies, effective communication and avoidance of allergens are critical to minimizing risk of allergic reactions. Apart from serious health effects, living with food allergies can significantly impact patient lifestyle, especially for children who are often excluded from group activities and peer relations.

WHAT ARE SOME KEY EFFORTS TO IMPROVE CARE AND MANAGEMENT OF FOOD ALLERGIES?

There are several components to successful management of food allergies (Box 1):

Box 1. Critical Aspects of Reducing Risk and Successful Management of Food Allergies

1. **Diagnosis:** does the patient have a food allergy? As many as up to 60% of food allergy sufferers may be misdiagnosed.
2. **Sensitivity:** how much allergen can an allergic individual tolerate before exhibiting an allergic response?
3. **Avoidance:** patients must follow avoidance diets that are in part dependent on truthful, accurate ingredient statements on packaged foods.
4. **Early exposure:** guidelines are evolving regarding exposure of infants to small doses of allergens such as peanut as a management tool.

Food allergy diagnosis can be done through a variety of methods including clinical history, skin prick, IgE test, and oral food challenges. Oral food challenges can be the most

informative of the tests, but they also carry the potential for an anaphylactic reaction and, as such, should be administered only under medical supervision in a clinical setting.

Food Allergy Research and Education (FARE) is working on developing standardized methods for conducting oral food challenges. Difficulties with oral food challenges include quantification of the amount and concentration of allergenic protein and what constitutes a clinical reaction. FARE has also established a nationwide allergy patient registry to better connect patient experiences with food allergy researchers and a clinical trial network of research institutions to collaboratively advance food allergy research.⁹

One promising research area involves developing allergy tests that do not subject patients to the anxieties and risks of ingesting allergenic foods (ie, oral food challenges). As an example, new research on substituting oral food challenges with a blood test *ex vivo* involves quantitative mapping of interactions of allergic protein epitopes with immune system components. This promising technology demonstrates that it is possible to monitor sensitivity over time, as well as patient response to treatment, without exposing patients to allergens.¹⁰ This work and its potential applications, however, address only the diagnosis of peanut allergy; expansion of this technology to other allergens requires further development and validation efforts. Nevertheless, *ex vivo* technologies hold promise for enhancing accuracy and speed of food allergy diagnosis as well as catalyzing the development of effective treatments.

WHAT IS THE CURRENT REGULATORY LANDSCAPE FOR ALLERGEN MANAGEMENT IN THE UNITED STATES?

The US Food and Drug Administration (FDA) plays a key regulatory role in allergy management via multiple centers within its structure. Notably, the Center for Food Safety and Applied Nutrition has a mission to ensure that the nation's food supply is safe, sanitary, wholesome, and honestly labeled. Regarding food allergens, the goal is ensuring that products containing allergens are properly labeled and identified by consumers (Box 2).

Box 2. US Regulations and Regulatory Activities Related to Food Allergies

- Implementing food allergen labeling laws
- Developing policy, guidance, and educational materials
- Developing analytical methods to detect allergens in different foods
- Inspection and compliance including recalls of products with undeclared allergens
- Expert scientific assessment of novel food ingredients, health claims, and risk assessments
- Reporting system (MedWatch) for problems with FDA-regulated products
- FALCPA, FSMA, and FASTER Acts are 3 regulatory milestones that help protect food-allergic consumers in the United States.

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A significant milestone in food allergen regulation is the passage of the US Food Allergen Labeling and Consumer Protection Act of 2004 (FALCPA). The Act required food manufacturers to state whether a food or an ingredient contains 1 or more of the 8 recognized major food allergens in the United States at the time: milk, eggs, fish, crustacean shellfish, tree nuts, peanuts, wheat, and soybean.¹¹ This list remained unchanged until April 23, 2021, when the Food Allergy Safety, Treatment, Education, and Research (FASTER) Act was signed into law, which added sesame to the list of food allergens recognized by the United States.² The Food Allergen Labeling and Consumer Protection Act applies to packaged food and dietary supplements; it does not apply to drugs, cosmetics, or foods sold in most retail/food service establishments. The Food Allergen Labeling and Consumer Protection Act does not address unintentional introduction of allergens into products by “cross-contact.” Manufacturers may voluntarily place allergen advisory or precautionary allergen labeling (PAL) statements (eg, “may contain”) to alert allergic consumers to the potential for allergen cross-contact. If used, the FDA requires such voluntary statements to be truthful and not misleading, and not used in lieu of good manufacturing practices.

In 2011, the FDA Food Safety Modernization Act (FSMA) was passed in part to address concerns with microbial and chemical hazards in food, including allergen cross-contact, and the final rule for preventive controls for human food was established in 2015. The rule stipulates that any firm using food allergens must establish and implement a food safety plan to control the risks and implement preventive controls, as well as ensure accurate labeling of finished food products. The rule, however, does not stipulate the establishment of thresholds for declaring when allergens are present in food by cross-contact.

The FASTER Act of 2021, which was supported and advocated for by food allergy non-governmental organizations (patient advocacy groups) such as FARE, requires sesame to be labeled on all food packaging starting January 1, 2023. By doing so, the Act provides support to approximately 1.6 million individuals who are allergic to sesame in the United States.¹²

The FASTER Act goes further by mandating reporting to Congress on collection of data on the prevalence and severity of food allergies, development of diagnostics tools, and development of new therapeutics to manage food allergies. It also mandates reporting on recommendations

and strategies to enhance these activities. These regulatory changes are significant and will likely accelerate research efforts on allergen management and treatment.

Going forward, the FDA has indicated that it will also foster global discussions on response thresholds, strategies for addressing allergen cross-contact, more informative labels, and education of the public and physicians about thresholds and allergenic risks in labeled foods.

HOW ARE RISKS OF FOOD ALLERGIES COMMUNICATED TO THE PUBLIC?

Potential exposure to food allergens is currently communicated first and foremost by the ingredient list. In the United States, all ingredients that have a functional or technical effect in the product must be declared on the label. In addition, a key element of the Food Allergen Labeling and Consumer Protection Act was the requirement to use plain English language to identify ingredients. For example, if caseinate is an ingredient, the label must indicate that it is from milk.

Potential exposure to food allergens is also communicated using PAL statements such as “may contain” or “packaged in a facility that also processes.” These statements have become common in labels of packaged foods (Figure). Precautionary allergen labeling statements may be useful for individuals with known low reactivity thresholds or who are concerned about any risk for allergic reaction because these individuals are keen on avoiding any potential allergen exposure. For most allergic individuals, however, these statements do not provide any information on how much allergen may be in the food, and thus, they do not aid in understanding the potential risk of exposure.^{13–15} This concern was highlighted in a 2017 report by the National Academy of Sciences, which recommended that the food industry, FDA, and the United States Department of Agriculture work together to replace the current ambiguous allergen labels with a risk-based approach that includes more information on the actual risks. The National Academy of Sciences Expert Panel found that current labeling practices for undeclared allergens are not effective and recommended “risk-based” labeling approach based on establishing response thresholds.¹⁴ It should be noted, however, that implementing this recommendation involves several challenges such as lack of uniformity of allergen residue distributed in food products and general lack of consumer awareness of their individual threshold doses.

CAN RESPONSE THRESHOLDS BE USED TO HELP MANAGE FOOD ALLERGENS?

A threshold is generally defined as the level that must be reached for a stimulus (in this case, food allergen) to cause a response (allergic reaction). Allergy thresholds can be estimated on an individual or population basis. They are potentially very informative on the hazards and risks of allergens

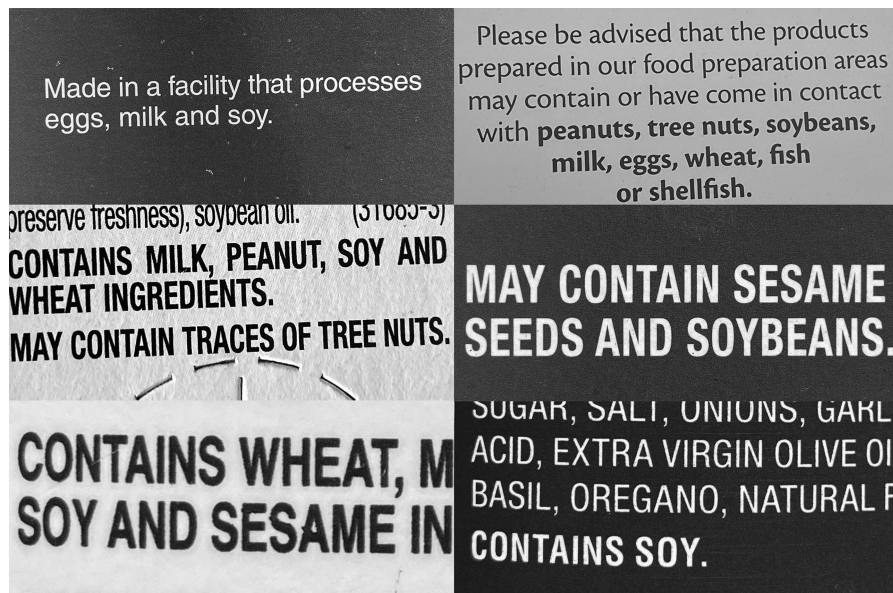


FIGURE. Examples of precautionary allergen labeling statements on packaged foods.

and, if derived from sufficiently large data sets, can be used to provide information on allergen exposure levels estimated to be relatively “safe” for most allergic individuals or on how much allergen can be tolerated by allergic individuals before they experience a reaction. Although the FDA is not required by law to establish threshold limits for food allergens, it may use published threshold information in certain regulatory determinations on a case-by-case basis. For example, products with undeclared allergens are classified into 3 classes (I, II, III) for recall determinations based on the likelihood of adverse effects, with class I having a reasonable probability for serious adverse health consequences or death. Undeclared major food allergens are generally considered to pose class I hazard because of risk for anaphylactic shock and potential fatality. It should be noted that almost all allergen recalls in the United States are class I recalls because they involve foods that have caused serious reactions in the past. Undeclared peanuts, for example, are always class I because peanuts are known to cause anaphylactic death. In contrast, undeclared wheat usually falls under class II recalls because the FDA is not aware of fatal allergic reactions to wheat. Class III reactions usually involve more minor labeling irregularities.

In certain recall scenarios, when exposure to an undeclared allergen is very low or unclear, information on thresholds may help determine whether risk of reaction from allergen exposure in the recalled product is reasonably likely or not to impact the health of allergic consumers.

The likelihood of adverse reactions is used to classify undeclared allergens for recall.

The FDA has in the past identified various approaches for establishing thresholds¹⁶ and has focused research on assessing and validating analytical threshold limits for a variety of food allergens. Food and Drug Administration scientists are currently developing methods to detect a variety of different allergens simultaneously to enhance understanding of allergen exposure risks in a variety of food products.

Significant progress has been reported in the broader scientific community for the establishment of response thresholds for a variety of food allergens. These thresholds are generally based on clinical assessment of eliciting dose responses in a population of allergic patients undergoing food challenges to increasing doses of allergens.^{17,18} If a sufficiently large sample size is used, the individual responses typically follow a sigmoidal dose distribution curve, which allows the identification of different response groups among the population including those who tolerate high doses (low sensitivity) and those who respond to low doses (high sensitivity). Quantitative risk analysis of challenge dose-response distributions for food allergens has already been used to identify reference dose limits for a voluntary, risk-based program for food manufacturers to use in assessing food allergen risks from cross-contact in Australia and New Zealand.¹⁹

The expanded use of allergen response thresholds has the potential to significantly improve food labeling with measurable benefits to allergic individuals. Achieving this goal, however, requires accurate clinical food challenge data for all food allergens and consensus on translating threshold data into actionable tolerance limits. It also requires an effort by medical providers to ensure that patients are aware of their own personal threshold doses. Equally

important, the success of this effort requires a focused effort to engage and educate consumers and the medical community public on thresholds and their use in allergy management.

CONCLUSIONS

Clear labeling of allergen hazards in products has improved the lives of allergic individuals. However, a fundamental risk management question remains unanswered for allergic individuals when consuming products with potential for allergen cross-contact: what constitutes a safe level of allergen within a food? Or stated another way, how much of the food with an undeclared allergen can be safely consumed? In the absence of guidance, PAL has been embraced as a primary management tool. However, current evidence shows that PAL is not particularly informative or helpful for patients because it does not adequately communicate allergenic risks in the product. This may lead on one hand to excessive dietary restrictions and unnecessary avoidance of potentially safe and nutritious food products. On the other hand, it may lead to greater mistrust and disregard for PAL and increased consumer risk-taking behaviors with products that may truly contain allergens and thus pose risk for adverse reactions. What is needed is a collaborative research effort to generate high-quality response threshold data for all allergens including ones not yet on the official list. Clinical trials should also be expanded to include representation of all ethnic backgrounds, ages, and sensitivity levels so that response thresholds are representative of the makeup of the US population. Results from these efforts are key to evidence-based decision making by regulators and the food industry. It should also be noted that the FDA can play a key role by moving to establish thresholds or reference doses for allergenic foods, thus providing the food industry some guidance and comfort level with the use of PAL. In addition, *ex vivo* research to eliminate oral food challenges should continue, along with research on effective treatments of food allergies. Finally, significant efforts should be devoted to communicating these findings and improving understanding of food allergies among healthcare providers and caregivers.

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