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Allergen Management as a Key Issue in Food Safety

António Raposo, Esteban Pérez, Catarina Tinoco de Faria,
and Conrado Carrascosa

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6.1 Introduction

Current food safety development not only takes into account microbiological, physical, and chemical food hazards, but also addresses the problem of food allergy because it has become a health problem due to the increasing prevalence and complexity of modern food and its globalization. In the last two decades, huge efforts have been made to assess the risk that arises from allergenic ingredients in food products for consumers with food allergy (Mourano et al., 2014b). Nevertheless, food allergy is an increasingly prevalent global health problem in both the industrialized world and in less developed countries, where, owing to poor labeling and awareness, a major challenge may exist (Gowland and Walker, 2015).

It is generally believed that food allergy affects 1%–2% of adults and up to 8% of children, which equates to 8 million food-allergic individuals in the European Union (EU) (Crevel, 2001), and 3%–5% of adults and 8% of children worldwide (Gupta et al., 2011; Sicherer, 2011). For most food-allergic individuals, the impact of their allergy affects their quality of life, with a small, but significant, number of people who suffer more severe reactions (anaphylaxis and death). Currently, the only way of treating food allergy is through elimination diet, where the offending food is avoided (Bruijnzeel-Koomen et al., 1995), for example, by hypoallergenic (low-allergen) foods, nonallergenic foods, or producing low-allergen foods by genetic modification. Thus, consumers with food allergies rely on food labels to disclose the presence of allergenic ingredients.

However, undeclared allergens can be inadvertently introduced into a food via cross-contact during manufacturing. However, allergen removal by cleaning shared equipment or processing lines has been identified as one of the critical points for effective allergen control (Jackson et al., 2008). For this reason, cleaning control and use of specific tests for allergens should systematically apply after cleaning and disinfection operations. Food handlers play a key role in the safety and hygiene of the food consumed by the public.

As at-risk consumers need to avoid culprit foods as ingredients and from cross-contamination with other foods, it is crucial to improve food handlers' allergen management competences when preparing and handling food.

There is a general duty of care in the food industry, with obligations set out in EU legislation to reduce and manage the presence of allergens, alongside other food hazards (Muraro et al., 2014b). For this reason, the EU has regulated mandatory information for consumers and all the establishments involved in the food chain through Regulation (EU) No. 1169/2011.

To support consumers with food allergies in avoiding food allergens, EU food legislation requires the allergenic food components used as ingredients to be labeled (Anandan and Sheikh, 2005). It also imposes general care duty in the food industry to reduce, manage, control, and communicate the presence of allergens, alongside other food hazards. This requires allergenic

ingredients to be managed rather than completely eliminated from the food supply (Ward et al., 2010). However, the majority of foods processed on shared equipment, and so-called allergen cross-contacts, may lead to the unintended presence of allergens (Muraro et al., 2014b). Yet when processing surfaces are shared with different ingredients or products either with or without allergens, there is every likelihood of allergen cross-contacts, even when they cannot be eliminated by proper cleaning.

The description of an allergen food profile implies the identification of all the potentially allergenic molecules that it contains. This statement takes for granted the concept that potential allergenic molecules represent a finite number of proteins, and the remaining components of the proteome of the allergenic source lack the features that cause the activation of the immune system, which leads to an allergic reaction (Ciardiello et al., 2013).

To date, the frequency and extent of cross-contact in commercial food items are generally unknown. As a result, precautionary allergen labeling, such as “may contain ...” is frequently used, partly for product liability reasons, but also to provide additional consumer safety information, even though the application of precautionary labeling may not be evidence based. In addition, major gaps in knowledge on the allergen risk management of manufactured food remain to be bridged (Muraro et al., 2014b).

These are typically classified as food allergies (i.e., reactions that involve the immune system) or food intolerances (i.e., reactions that do not involve the immune system). Allergen terminology has been published by the World Allergy Organization (WAO) and is based on the terminology originally proposed by the European Academy of Allergy and Clinical Immunology (EAACI).

A food allergy occurs when an allergen (i.e., a protein in a food, which will not produce an adverse reaction in the majority of people) sets off a chain of reproducible reactions that involve the immune system. Reactions can either be antibody or cell mediated. The former is more frequent and occurs in two stages:

1. *Sensitization*: Initial contact with an allergen does not evoke an allergic reaction, but primes the immune system.
2. *Reaction*: Once sensitization has occurred, subsequent exposure to that allergen can lead to an allergic reaction; that is, in a sensitized individual, allergenic protein cross-links with the immunoglobulin E (IgE) antibodies on the surface of mast cells cause the release of histamine or other substances, such as leukotrienes and prostaglandins.

Food intolerances do not involve the immune system. Food intolerances may be categorized as enzymatic (e.g., due to an enzyme deficiency, such as

lactase, required to digest milk sugar lactose) or pharmacological (e.g., due to amines, such as histamine), or the mechanism may be undefined in some cases (Sadler et al., 2013).

In reference to food allergen regulation and labeling, a number of countries and regulatory bodies have recognized the importance of providing this information by enacting laws, regulations, or standards for food allergen labeling of “priority allergens.” However, different governments and organizations have taken different approaches to identify these priority allergens and to design labeling declaration regulatory frameworks (Gendel, 2012). The development of labeling regulations for food allergens has been complex given the number of foods that are allergens, the range of sensitivities in the allergic population, and the variety of ways that allergenic foods and their derivatives are used as ingredients. So after extensively searching regulatory databases, agency and government websites, literature citations, and references in other regulatory documents, it is not surprising that Gendel (2012) identified 19 laws, directives, regulations, rules, and ministerial statements on food allergen labeling.

European food law aims to reach a high level of protection of human health and consumers’ interests. Article 8 of Regulation (EC) No. 178/2002 prohibits adulteration of food and any fraudulent, deceptive, or other practices that mislead consumers. Likewise, the United States has regulated the Allergens and Ingredients of Public Health Concern: Identification, Prevention and Control, and Declaration through Labeling.

Article 14 prohibits unsafe food from being sold, such as food injurious to health, including the particular health sensitivities of any specific category of consumers (but not exclusively people with food allergy) where food is intended for that category of consumers (Gowland and Walker, 2015). Other EU legislation (European Directive 2007/68/EC) that amends Directive 2000/13/EC, the labeling of 13 allergenic foods (or food groups) and derived products thereof, as specified in Annex IIIa of Directive 2007/68/EC, is mandatory when used as ingredients for prepacked foods, regardless of the concentration of the potentially allergenic ingredient. The 14 allergenic foods (or food groups) include the most important foods that cause IgE-mediated and non-IgE-mediated allergies, celiac disease, and nonallergic food hypersensitivities. The sulfur dioxide and sulfites also listed in this directive cause intolerances. Certain products derived from the foods on the list may be exempted from labeling requirement if they can be assessed and found to be nonallergenic. For example, wheat-based glucose syrups, including dextrose or maltose, do not require labeling. Other exceptions are fish gelatin used as a carrier for vitamins or carotenoids, fully refined soya bean oil, and alcoholic distillates derived from nuts.

More specifically, Regulation 1169/2011 addresses allergen avoidance risks relating to composition, labeling, and food safety. The inclusion in prepacked food of any of 14 major allergens defined by Annex II to Regulation 1169/2011 (replacing Annex IIIa to Directive 2000/13/EC) triggers, with certain limited

exemptions, specific labeling requirements—14 extended on December 13, 2014, to nonprepacked food, including catering establishments.

Regarding the undeclared allergen trends observed in the U.S. industry, the Food Safety and Inspection Service (FSIS) has recognized a notable increase in the number of recalls (from 13% in 2008 to 35% in 2012) that have occurred because of undeclared allergens and ingredients of public health concern in products. U.S. regulations only recognize eight allergens: wheat, crustacean shellfish (e.g., shrimp, crab, and lobster), eggs, fish, peanuts, milk, tree nuts (e.g., almonds, pecans, and walnuts), and soybeans. More than 170 foods have been reported to cause allergic reactions, although eight of the most common allergenic foods account for 90% of all food allergic reactions, and are the sources from which many other ingredients are derived (FSIS, 2015).

The FSIS has found that many of these recalls occurred because of a change in product formulation by establishing or making changes in a supplier's ingredient formulation that was not reflected on the labeling of the finished meat or poultry product. If an establishment recalls a product because of an undeclared ingredient, it has likely failed to (1) address the chemical (allergen) food safety hazard in its hazard analyses, (2) support the decisions made in hazard analyses, (3) reassess hazard analyses, and (4) effectively implement controls to support the decisions made in hazard analyses (see 9 CFR 417.2(a)(1), 417.5(a)(1), 417.4(a)(3), and 417.3(b), respectively), (FSIS, 2015). Establishments are required to declare ingredients on labels if they are included in the product formulation (9 CFR 317.2 and 381.118). Allergen-containing products must be properly handled, processed, formulated, and stored. If allergens are not declared, then the product is adulterated and misbranded. If an adulterated and misbranded product has already been shipped to commerce, the FSIS would request its recall.

Since 2004, the U.S. Food Allergen Labeling and Consumer Protection Act (FALCPA) requires any products under the jurisdiction of the Food and Drug Administration (FDA) to contain a major food allergen to clearly identify the allergen on labels (Public Law 108-282, Title II). The FSIS supports the voluntary addition of allergen statements (e.g., "contains" statements) on meat and poultry product labels immediately following the ingredients statement discussed in the FSIS Compliance Assistance: Allergens—Voluntary Labeling Statements. Nevertheless, advisory labels are not regulated by FALCPA, and the type of tree nut, shellfish, or fish does not need to be disclosed on the advisory label (FSIS, 2015).

All the ingredients used in the formulation of meat, poultry, or egg products must be declared by their common or usual name on the ingredients statement. Occasionally, a substance may be used in a meat, poultry, or egg product whose use in that product, which is consistent with the FDA's labeling definition, would be taken as an incidental additive or processing aid (21 CFR 101.100(a)(3)). If an establishment suspects that a substance is a processing aid or incidental additive in a meat, poultry, or egg product, it should

contact the FSIS to determine its suspicion. The FSIS makes these determinations on a case-by-case basis, as discussed in the FSIS Compliance Guide on the Determination of Processing Aids (FSIS, 2015). Despite the improvements made in labeling according to FALCPA, limitations in the law may impose continued challenges for consumers with a food allergy.

In addition to problems in the food industry, the Food Allergen Act itself fails to include provisions that would protect allergic consumers more effectively (Grossman, 2015). For example, requirements of the act apply only to packaged foods regulated by the FDA, so consumers who buy bulk foods and foods not in packaged form may not be informed adequately (Grossman, 2015). In addition, the act does not require labeling of allergens in restaurant food, nor does it regulate the use of advisory warnings about the possible presence of allergens (Derr, 2006). These limitations mean that some consumers, who are not fully informed, may consume food allergens and risk serious allergic reactions (Roses, 2014).

6.2 Overview of Food Allergies

Food is essential for life, a major source of pleasure, and often intrinsic to our cultural identity. Most individuals eat three meals a day, plus snacks, and typically consume some food at most social gatherings. The average person in Westernized societies is likely to eat 2–3 tons of food in one's lifetime. Consequently, it is not surprising that food is so frequently implicated in a variety of maladies, and that it causes so much distress in individuals who believe they are afflicted with food allergy (Sampson, 1999). Some of the controversy that surrounds food allergy has stemmed from disparate use of terms. In an attempt to confer uniformity to the nomenclature related to food allergies, the EAACI proposed a mechanistic classification of these disorders (Bruijnzeel-Koomen et al., 1995). Adverse food reactions are defined as any aberrant reaction after ingesting food or food additive. Adverse food reactions may be the result of toxic or nontoxic food reactions. Toxic reactions can occur in anyone, provided a sufficient dose is ingested (e.g., histamine in scombroid fish poisoning). Nontoxic reactions depend on individual susceptibilities and may be the result of immune mechanisms (allergy or hypersensitivity) or nonimmune mechanisms (intolerance), or in the majority of cases, may arise through unknown mechanisms (Ortolani, 1995; Sampson, 1999; Dupont, 2011; Sicherer and Leung, 2011; Vickery et al., 2011; Waserman and Watson, 2011; Muraro et al., 2014c). According to the National Institute of Allergy and Infectious Diseases (NIAID)–sponsored guidelines, food allergy is an “adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” (Boyce et al., 2010). This definition encompasses immune responses that are IgE mediated, non-IgE

mediated, or a combination of both, and is in agreement with other international guidelines (Sackeyfio et al., 2011; Urisu et al., 2011). Food allergy is an increasingly prevalent global health problem in both the industrialized world (Ring et al., 2001; Nwaru et al., 2014) and less developed countries, where, owing to poor labeling and awareness, a very significant challenge may exist. There are well-documented detriments to the quality of life of allergic consumers and their families (Avery et al., 2003; King et al., 2009). A systematic review by RAND Corporation was performed by using prespecified criteria directed toward obtaining articles on epidemiologic aspects of food allergy (Schneider Chafen et al., 2010). It concluded that food allergy affected from 1% to 2% and up to 10% of the population (Chafen et al., 2010).

Theoretically, any food that contains protein would be capable of eliciting an allergic reaction, although the likelihood of foods provoking allergic sensitization vastly varies. The Codex Committee on Food Labelling established, after considerable debate, a list of the most common allergenic foods associated with IgE-mediated reactions on a worldwide basis, which includes peanuts, soybeans, milk, eggs, fish, crustacea, wheat, and tree nuts. This list was presented to the Codex Alimentarius Commission and was adopted in 1999 at its 23rd session (FAO and WHO, 2001). These commonly allergenic foods account for more than 90% of all moderate to severe allergic reactions to foods, although an extensive literature search has revealed that more than 160 foods are associated with sporadic allergic reactions (Hefle et al., 1996). Celery, mustard, sesame, lupine, and molluscan shellfish have been identified as significant allergens in European countries (Regulation 1169/2011), and buckwheat is also a common allergen in Japan (Akiyama et al., 2011).

Allergy to cow's milk, egg, wheat, soy, peanut, tree nuts (like walnut, almond, hazelnut, cashew, pecan, pistachio, and Brazil nut), fish, and shellfish constitutes the majority of food allergy reactions across different age groups and regions in Europe (Nwaru et al., 2014). In general, these allergies tends to occur in childhood (Patel and Volcheck, 2015).

Annex II of Regulation 1169/2011, on the provision of food information to consumers, mentions a list of substances or products that cause allergies or intolerances in relatively wide population groups. The list includes cereals that contain gluten, crustaceans, eggs, fish, peanuts, soybeans, milk, nuts, celery, mustard, sesame seeds, sulfur dioxide and sulfite, lupin, and mollusks.

According to the Food and Agriculture Organization (FAO, 1995) of the United Nations, these foods or food groups are widely considered to comprise commonly allergenic foods.

6.2.1 IgE-Mediated Food Allergies

The most common type of food allergy is mediated by allergen-specific IgE antibodies (FAO and WHO, 2001). IgE-mediated reactions are known as immediate hypersensitivity reactions because symptoms occur within

minutes to a few hours of ingesting the offending food. These type of allergies affect perhaps 10%–25% of the population in developed countries (Mekori, 1996), although food allergies represent a small fraction of all allergic diseases. Infants and young children are more commonly affected by IgE-mediated food allergies than adults; the prevalence among infants under the age of 3 may be as high as 5%–8% (Bock, 1987; Sampson, 1990; European Commission, 1998).

In IgE-mediated food allergies, exposure to a specific food and the proteins contained therein elicits the development of food allergen-specific IgE antibodies (sIgE). These IgE antibodies attach to the surfaces of mast cells and basophils, and thus sensitize the individual to react upon subsequent exposure to the specific food. Therefore, to become sensitized, individuals must first be exposed to the food in question. Some food proteins are more likely than others to elicit allergic sensitization. Information on levels of exposure to a food that are minimally necessary to illicit allergic sensitization in susceptible individuals is extremely limited (FAO and WHO, 2001). IgE-mediated food allergies may result in the rapid onset of severe reactions (usually within 2 hours of oral exposure to a given food), which may be manifested by a variety of signs and symptoms that can involve the gastrointestinal tract (vomiting and abdominal pain), airways (persistent cough, hoarse voice, wheeze, stridor, respiratory distress, and nasal congestion), circulatory system (pale and floppy infant or young child, hypotension, or collapse), or skin (urticaria, angioedema, erythema, and pruritus) (Boyce et al., 2011; Burks et al., 2012). The severity of reactions varies from mild (e.g., hives) to severe (e.g., anaphylaxis). Subjects can have allergic sensitization (production of specific IgE antibodies) to food allergens without presenting clinical symptoms of an allergic reaction on exposure. Thus, sensitization alone does not suffice to define food allergy. An sIgE-mediated food allergy requires both the presence of sensitization and the development of specific signs and symptoms upon exposure to that food (Boyce et al., 2011). The severity of allergic reactions varies according to the amount of ingested food, coingestion of other foods, and food preparation (cooked, raw, or processed) (Boyce et al., 2011). Severity can also be influenced by patient age, and by absorption rapidity, which can be influenced by whether food was eaten on an empty stomach or close to doing exercise. Although reactions after a severe reaction are also likely to be severe (Vander Leek et al., 2000), mild reactions can also be followed by more severe reactions (Ewan and Clark, 2001).

Food-induced anaphylaxis is a serious allergic reaction with a rapid onset, and it can even cause death (Sampson et al., 2005). IgE-mediated food-induced anaphylaxis involves a systemic mediator release from sensitized mast cells and basophils. In patients with food-dependent, exercise-induced anaphylaxis, whether a reaction occurs depends on the amount of time between food consumption and exercising, usually within 2 hours.

All IgE testing for food allergies must be interpreted in the context of the patient's clinical reactions. Many patients will have positive IgE tests to foods despite never having a clinical reaction. IgE will also remain positive if they once had food allergies, but have since developed tolerance (Kurowski and Boxer, 2008). The most widely used method to assess for food-specific IgE is the skin prick test (SPT). In such tests, a portion of the commercial food extract in question is pushed into the epidermis with a needle or probe, and the area is observed for a wheal and flare reaction after 15–20 minutes. Some allergists believe that fresh extracts of fruits and vegetables have superior sensitivity and specificity, and use them in SPT. Although generalized reactions rarely occur (overall rate of about 0.05%), no deaths have been reported after SPT (Devenney and Fäith-Magnusson, 2000). Serum sIgE levels can be measured by immunoassays (ImmunoCAP and Immulonite) which provide reliable and reproducible measurements, although results can take hours to days. SPTs are quick and simple to perform. SPT wheal size correlates with the likelihood of clinical allergy (Knight et al., 2006; Sicherer and Sampson, 2006), and 95% positive predictive thresholds (wheal size above which there is a >95% chance of clinical allergy) have been described for common allergens (Sampson, 2001; Roberts and Lack, 2005). However, wheal sizes can vary as a result of age, diurnal variation, body site at which SPT is performed, skin reactivity, and the SPT device and reagents used. Therefore, 95% positive predictive values (PPVs) established in a specific clinical setting might not be applicable to different populations and settings.

6.2.2 Clinical Spectrum of IgE-Mediated Food Allergies

6.2.2.1 Anaphylaxis

Anaphylaxis symptoms occur in multiple organ systems and can include throat swelling, wheezing, rhinorrhea, urticaria, hypotension, and abdominal cramping (Nowak-Wegrzyn and Sampson, 2006). Risk factors for death from anaphylaxis are adolescent or young adult patients; underlying asthma; allergies to crustaceans, tree nuts, peanuts, or fish; and a delay in or lack of administration of epinephrine.

6.2.2.2 Acute Urticarial

Food allergies account for 30% of acute urticaria cases (Legrain et al., 1990). Patients become symptomatic within minutes to hours of eating the provoking food. As acute urticaria can be one manifestation of anaphylaxis, care to identify symptoms in other organ systems that would lead to raising the diagnosis to this more urgent level is warranted. Chronic urticaria is much less commonly caused by food allergies (3%–4% of cases) (Kulthanan et al., 2007).

6.2.2.3 Atopic Dermatitis

About 35% of children with atopic dermatitis have a food allergy, based on double-blind, placebo-controlled food challenges (Eigenmann et al., 1998). Skin manifestations improve when suspected foods are removed from the diet; eggs, milk, and peanuts are more commonly implicated. In breast-fed infants, the elimination of suspected foods in the mother's diet has led to clinical improvement.

6.2.2.4 Oral Allergy Syndrome

Oral allergy syndrome is the most common food allergy, as it is clinically recognized in up to 10% of patients who have allergic rhinitis or asthma from grass, weed, or tree pollen (Ma et al., 2003). However, it is believed to have a significantly higher prevalence in patients with birch pollen allergy (Ghunaim et al., 2005). Oral allergy syndrome manifestations are brief in duration, limited to the mouth and throat, and are sometimes so mild that the patient may not seek evaluation. Proteins similar to the aeroantigens to which the patient is sensitive are present in apples, carrots, and cherries (birch pollen); kiwi and tomato (grass pollen); and melons (ragweed pollen). When these foods come into contact with the oropharynx, a local reaction occurs.

6.2.3 Mixed IgE- and Non-IgE-Mediated Food Allergies

Diagnosing mixed IgE- and non-IgE-mediated food allergies is more challenging than diagnosing IgE-mediated food allergies. The approach begins with the clinical history. A clear cause and effect between food ingestion and symptoms might not exist because the symptoms of such food allergies are typically chronic rather than immediate. If the clinical history is not definitive, diagnosis can usually be made by food elimination, followed by reintroduction challenge. Food challenges can also be performed to assess when the disease has been outgrown (Sackeyfio et al., 2011). Home introduction challenges can be undertaken if the sIgE test result is negative and food protein-induced enterocolitis syndrome is not suspected. Non-IgE-mediated immunologic reactions (e.g., cell mediated) include food protein-induced enterocolitis, proctocolitis, and enteropathy syndromes. These conditions primarily affect infants or young children who present abdominal complaints, such as vomiting, abdominal cramps, diarrhea, and occasionally blood in stools, and failure to thrive or poor weight gain. Examples of food allergy comorbidities with mixed IgE- and non-IgE-mediated causes include eosinophilic esophagitis and atopic dermatitis (Boyce et al., 2011). Allergic eosinophilic esophagitis, gastritis, and gastroenteritis are characterized by infiltration of the esophagus, stomach, and/or intestinal walls with eosinophils, basal zone hyperplasia, papillary elongation, the absence of vasculitis,

and peripheral eosinophilia in about 50% of patients. An eosinophilic infiltrate may involve the mucosal, muscular, and/or serosal layers of the stomach or small intestine, and clinical symptoms correlate with the extent of eosinophil infiltration of the bowel wall (Katz et al., 1977; Moon and Kleinman, 1995). Eosinophilic infiltration of the muscular layer leads to thickening and rigidity, which provokes obstruction symptoms, whereas infiltration of the serosal area results in ascites that contain eosinophils. Allergic eosinophilic esophagitis is most frequently seen in infancy and through to adolescence, and presents chronic reflux (gastroesophageal reflux), intermittent emesis, food refusal, abdominal pain, dysphagia, irritability, sleep disturbance, and failure to respond to conventional reflux medication.

Dietary protein enterocolitis syndrome is the disorder most frequently seen in the first months of life when infants first present irritability, protracted vomiting, and diarrhea, which frequently results in dehydration (Powell, 1976, 1978). Vomiting generally occurs 1–3 hours after feeding, and continued exposure may result in bloody diarrhea, anemia, abdominal distention, and failure to thrive. Symptoms are most commonly provoked by cow's milk or soy protein-based formulas, but occasionally result from food proteins passed in maternal breast milk. A similar enterocolitis syndrome has been reported in older infants and children, and is caused by egg, wheat, rice, oat, peanut, nut, chicken, turkey and fish sensitivity (Sicherer et al., 1998). Hypotension occurs in about 15% of cases after allergen ingestion (Goldman et al., 1963; Sicherer et al., 1998). In adults, shellfish (e.g., shrimp, crab, and lobster) sensitivity may provoke a similar syndrome with severe nausea, abdominal cramps, and protracted vomiting.

6.2.4 Characteristics of Patients with Food Allergies

Most patients with food allergies have an atopic disorder. However, only 10% of patients with atopic disorders have food allergies (Dreskin, 2006). A family history of food allergy or other atopic disorders increases the risk of developing food allergy. Genetic predisposition, including specific haplotypes, has been identified for some common food allergies. Oral allergy syndrome is confined to patients with allergic rhinitis or asthma. The majority of children outgrow the most common food allergies; those who do not will have persistent allergies to the same or different foods. Approximately 70% of children with egg allergy and 85% with milk allergy will outgrow them by the age of 5 (Host et al., 2002; Ricci et al., 2006). However, about 40%–60% of these children will develop asthma and 30%–55% will develop allergic rhinitis (Host et al., 2002; Ricci et al., 2006). Risk of persistent allergy to peanut is much greater, with only 20% of children ever developing tolerance (Moneret-Bautrin and Morisset, 2005). Adolescents with persistent allergies and adults with new onsets are particularly prone to fatal food allergies. Increased risk in adolescents may be explained by their tendency to eat foods that could contain allergens and to not

carry epinephrine with them (depending on their social situation) (Sampson et al., 2006). Adults with food allergies usually remain allergic.

6.2.5 Traceability of Allergenic Foods in the Food Chain Supply

Over the last two decades, allergenic foods have become recognized as a food safety hazard. During the same period, knowledge about the biology and clinical characteristics of food allergy has grown, together with information that can be used to assess the risk more accurately (Ward et al., 2010). Allergen management has evolved in line with growing knowledge and increased understanding of the issue. Initially, very little was known about the key determinants of risk; industry's approach to date has been based on existing good manufacturing practices (GMPs) by ensuring the segregation of allergenic ingredients and the systematic declaration of allergens on labels where mandated. However, much more needs to be done to minimize risks and provide allergic consumers with consistent risk communication and a wide choice of products. Developing knowledge about the relationship between allergen doses and population reactivity, and the tools to translate this knowledge into practical action to improve the safety and quality of life of allergic consumers, means that it will now be possible to manage food allergens as effectively as other food safety hazards (Hattersley et al., 2014).

Historically, multiple approaches have been considered to assess the risk from low-level residues of allergenic foods that might accidentally be present in other foods (Taylor et al., 2002; Threshold Working Group, 2008; Madsen et al., 2009; Taylor and Baumert, 2010). Similar approaches could equally be applied to the consideration of risk to allergic consumers posed by deliberate low-level allergenic ingredients. Few regulatory bodies have addressed the food allergen risk assessment and risk management issue. However, the UK Food Standards Agency (FSA, 2006) has published qualitative guidance to help food businesses to consider where allergen cross-contact risks could arise and how they might be better managed. Faced with uncertainty as to the risk and lack of quantitative guidance, many food manufacturers opt to use some form of precautionary labeling to alert allergic consumers to the possibility of and, consequently, the risks from the inadvertent presence of allergenic food constituents in a variety of phrases (Hattersley et al., 2014). While the intention of such warnings is to help allergic consumers to make safe food choices, the use of such warnings has become widespread, and it can be difficult to find examples of certain food product groups without them (FSA, 2002; Sakellariou et al., 2010; Barnett et al., 2011a; Zurzolo et al., 2012). Faced with the resulting uncertainty, manufacturers often feel obliged to provide these additional voluntary warnings where they qualitatively determine that any risk may exist, no matter how low or remote. An evidence-based approach that leads to the definition and adoption of quantitative allergen management reference doses would result in consistency and transparency in risk management decision making, and subsequent consumer and clinician

risk communication. This would, in turn, allow us to clearly discriminate between foods and their suitability for allergic consumers, and would therefore improve food allergy management. However, before this goal can be reached, a number of data gaps need to be bridged, including the lack of characterization of the allergen hazard (dose distribution curves) (Crevel et al., 2008; Threshold Working Group, 2008; Madsen et al., 2009) and the relative insensitivity and lack of robustness of some analytical methods (Poms and Anklam, 2004; Diaz-Amigo and Popping, 2010). Recognition that consistent risk management approaches with agreed quantitative reference doses based on scientifically robust principles will provide optimal consumer risk protection has grown. In parallel, all stakeholder groups now recognize that a zero risk is unrealistic (Madsen et al., 2010, 2012). Indeed, the EU food safety law explicitly enshrines risk analyses as one of its foundations (European Union, 2002). These risk management approaches are founded on an understanding that minimizing risk from allergenic foods is a responsibility shared across stakeholders (patients, clinicians, food manufacturers, retailers, caterers, and regulators). Industry's current approach to allergen management encompasses existing GMPs as part of a classic Hazard Analysis and Critical Control Point (HACCP) approach (Codex Alimentarius Commission, 1997), including traceability through the supply chain, segregation of allergenic ingredients, and application of "allergen cleans," to ensure the production of accurately labeled safe food. A "visually and physically clean" standard for processing and manufacturing the operations control of allergen cross-contamination, based on thorough visual inspections of the production line (following cleaning) and of the final product, has been shown to provide a practical and effective risk management approach (Jackson et al., 2008), and does away with the need for allergen on-line detection methods. Despite these stringent measures, the industry recognizes that it still needs to do more.

6.2.6 Development of Allergen-Free Foods

Although some studies have offered promising results for the successful induction of oral tolerance for certain allergens (Clark et al., 2009; Staden et al., 2007), a general causative immunotherapy for food allergy is currently not available (Sicherer and Sampson, 2006). Consequently, the treatment of food allergies requires strictly avoiding offending food allergens (De Blok et al., 2007; Sampson, 2004). Therefore, the reliable labeling of allergenic constituents is of paramount importance, which is not yet fully available. Labeling the most common allergenic foods that are added as ingredients in prepackaged foods has improved thanks to regulatory amendments, such as the EU Labeling Directive 2007/68/EC and the U.S. FALCPA (European Commission, 2007; FDA, 2004). The lack of legal thresholds for adventitious contamination with allergens, the so-called "hidden" allergens, is a constant challenge for consumers with food allergies. For food manufacturers, these hidden allergens represent a problem that is difficult to control. Very little is known about

the extent and frequency of cross-contamination, and producers are challenged to decide on the use of precautionary labeling. To limit advisory labeling to products, if necessary, food manufacturers require sound knowledge about the frequency and extent of allergen cross-contamination while manufacturing ingredients and retail packaged goods. Depending on the application of cleaning between product changes and the availability of analytical testing to verify cleaning efficiency, qualified allergen sanitation procedures may be established and precautionary labeling can thus be avoided.

U.S. Agriculture Secretary Tom Vilsack announced on June 24, 2014, a new report on discoveries by the U.S. Department of Agriculture (USDA) researchers, which have led to new patents and inventions with the potential for commercial application and potential economic growth. The USDA innovations in this annual report include USDA-supported research that could offer solutions for millions who suffer allergies from peanuts and wheat. Highlighted discoveries from the USDA's 2014 Technology Transfer Report include procedures to remove up to 98% of allergens from peanuts without affecting flavor (USDA, 2015).

6.3 Overview of Food Intolerances

Food intolerances are often confused by the general public with food allergies, and vice versa. The difference between them for the scientific community is clear, but that is not the case when we focus on food intolerances: the point is that no consensus has been reached in the scientific community as to what are and are not intolerances, and whether this term is correct.

According to the WAO, no agreement on allergen nomenclature intolerance exists (Johansson et al., 2003). The nomenclature agreement is based on mechanisms. Hypersensitivity is either nonimmunological or immunological, that is, allergy. Allergy can be either IgE mediated or due to other mechanisms. Despite the fact that allergists do not use intolerance to describe allergy or allergic diseases, the word *intolerance* is used by gastroenterologists and laypersons, which should be discussed in this context. The term *intolerance* should be better defined and restricted to some nonimmunological or nonallergic diseases (Dreborg, 2015).

For other authors (Vandenplas, 2015a), *intolerance* is a term loaded with different meanings and interpretations. Intolerance, or hypersensitivity, relates to all reactions to foods, while allergy indicates that an immune mechanism is involved and atopy is the terminology for IgE-mediated reactions.

Adverse reactions to food are divided into toxic reactions and nontoxic reactions. The occurrence of nontoxic food reactions depends on individual susceptibility to a certain food. Nontoxic adverse reactions to food are either immune mediated or non-immune mediated. For non-immune-mediated

reactions, the term *food intolerance* is recommended, while immune-mediated reactions are referred to as *food allergies* (Bruijnzeel-Koomen et al., 1995).

It is possible to classify food intolerances into enzymatic, pharmacological, and undefined food intolerances. Secondary lactase deficiency affects most of the adult world population, whereas the majority of other enzyme deficiencies are rare inborn errors of metabolism. Pharmacological food intolerance is present in individuals who are abnormally reactive to substances, such as vasoactive amines (like histamine), which are normally present in some foods (Bruijnzeel-Koomen et al., 1995).

The *food intolerance* term also includes confirmed adverse reactions to food for which the offending mechanisms are unknown (Bruijnzeel-Koomen et al., 1995).

6.3.1 Gluten “Intolerance”

Gluten is the main structural protein complex of wheat, with equivalent toxic proteins found in other cereals, including rye and barley. The toxic protein fractions of gluten include gliadins and glutenins, with gliadins containing monomeric proteins and glutenins containing aggregated proteins (Sapone et al., 2012). Possibly the introduction of gluten-containing grains, which occurred about 10,000 years ago with the advent of agriculture, represented an evolutionary challenge that created conditions for human diseases related to gluten exposure, the best known of which are mediated by the adaptive immune system: wheat allergy and celiac disease. For both conditions, the reaction to gluten is mediated by T-cell activation in gastrointestinal mucosa.

Gluten-sensitive enteropathy, *celiac sprue*, and *nontropical sprue* are terms sometimes used to describe celiac disease. The term *celiac disease* is more commonly used and accepted (Anderson and Berrill, 2016).

According to the European Food Information Council (EUFIC, 2012) and the Coeliac UK organization (2016), celiac disease is not an intolerance in the strict sense, nor is it a food allergy: it is an autoimmune reaction.

Besides celiac disease and wheat allergy, there are cases of gluten reactions in which neither allergic nor autoimmune mechanisms are involved. These are generally defined as gluten sensitivity (Brandtzaeg et al., 1989; Catassi and Fasano, 2008; Anderson et al., 2012). Some individuals who experience distress when eating gluten-containing products and show improvement when following a gluten-free diet may have gluten sensitivity instead of celiac disease. Gluten-sensitive patients are unable to tolerate gluten and develop an adverse reaction when eating gluten that usually, and unlike celiac disease, does not lead to damage in the small intestine (Sapone et al., 2012).

Celiac disease affects 0.6%–1.0% of the world’s population (Fasano et al., 2003; Hoggan, 2011), with wide regional differences in Europe (e.g., the prevalence is 0.3% in Germany and 2.4% in Finland) for reasons that remain unclear (Mustalahti et al., 2010). Celiac disease is also common in developing

countries, particularly in North Africa (Alarida et al., 2011) and the Middle East (Dalgic et al., 2011).

Celiac disease prevalence increases under at-risk conditions, such as a family history of celiac disease, autoimmune diseases, immunoglobulin A (IgA) deficiency, some genetic syndromes (Down, Turner, and William syndromes), and especially type 1 diabetes and thyroiditis (Sapone et al., 2012).

Serologic screening studies have shown that only a small proportion of cases of celiac disease are clinically recognized (21% according to a recent European study) (Mustalahti et al., 2010). Prevalence is 1.5–2 times as high for both women and men. Celiac disease affects all age groups, and its main symptoms are malabsorption, chronic diarrhea, steatorrhea, flatulence, and weight loss or failure to thrive (Motala, 2004).

The clinical features of celiac disease are protean and reflect its systemic nature. Frequent symptoms and signs also include abdominal distention (in 40%–50% of patients). Other manifestations include iron deficiency with or without anemia, recurrent abdominal pain, aphthous stomatitis, short stature, high aminotransferase levels, chronic fatigue, and reduced bone mineral density (Green and Cellier, 2007). Unusual manifestations of celiac disease include dermatitis herpetiformis, a blistering rash with pathognomonic cutaneous IgA deposits (Caproni et al., 2009; Salmi et al., 2011).

Patients with celiac disease are sensitive to gliadin, the alcohol-soluble portion of gluten found in wheat, oat, rye, and barley. Regarding pathology, celiac disease is a dietary protein enteropathy characterized by villous atrophy and inflammatory cell infiltrate. Celiac disease is associated with the HLA-DQ2 (and DQ8) haplotype. About 90% of patients with celiac disease possess IgA anti-gliadin and antiendomysium antibodies. Endoscopy typically reveals profound villous atrophy and extensive cellular infiltrate (Motala, 2004).

The clinical spectrum of celiac disease is wide and includes symptomatic cases with either classical intestinal (e.g., chronic diarrhea and weight loss) or nonclassical extraintestinal (e.g., anemia, osteoporosis, and neurological disturbances) features, and silent forms that are occasionally discovered in serological screening (Sapone et al., 2012).

The pathogenesis of celiac disease involves an external trigger (gluten), changes in intestinal permeability, enzymatically modified gluten, human leukocyte antigen (HLA) recognition, and innate and adaptive immune responses to gluten peptides that involve self-antigens (e.g., transglutaminase), and eventually lead to celiac enteropathy (Jabri and Sollid, 2009; Schuppan et al., 2009).

Gluten ataxia is a sporadic form of ataxia with positive serologic markers for gluten sensitization (although the association with celiac disease is still debated) (Hadjivassiliou et al., 2008). Celiac crisis is a rare life-threatening syndrome, mostly observed in children, characterized by severe diarrhea, hypoproteinemia, and metabolic and electrolyte imbalances.

Complications associated with untreated celiac disease include osteoporosis, impaired splenic function, neurologic disorders, infertility or recurrent abortion, ulcerative jejunoileitis, and cancer (Fasano and Catassi, 2001). Enteropathy-associated T-cell lymphoma and adenocarcinoma of the jejunum are rare complications of celiac disease (Sharaiha et al., 2012).

6.3.2 Lactose Intolerance

Lactose is a disaccharide of glucose and galactose. It is abundant in mammalian milk, sometimes called milk sugar, and is essential for nourishing newborn infants (Bender, 2009; Mattar et al., 2012).

The most common type of carbohydrate maldigestion and malabsorption is caused by intestinal lactase enzyme deficiency. Lactose malabsorption or hypolactasia is a common condition caused by poor lactase activity (Vandenplas, 2015b).

In most infants, intestinal lactase activity is maximal during the perinatal period. However, after 2–12 years of age, two distinct groups emerge: a “lactase nonpersistence” group with poor lactase activity (hypolactasia) and a “lactase persistence” group of individuals who retain their neonatal level of lactase activity into adulthood (Troelsen, 2005; Rasinperä et al., 2004).

Hypolactasia does not cause any disturbance or discomfort, unless lactose-containing food is consumed. Colonic microflora ferment undigested lactose in the intestinal lumen, which leads to the production of short-chain fatty acids, hydrogen, carbon dioxide, and methane, which are responsible for clinical manifestations (Mattar et al., 2012).

Nonpersistent lactase (natural decline in intestinal lactase that leaves adults minimally able to digest lactose) is poorly associated with so-called “lactose intolerance” (symptoms that result from the ingestion of lactose, including flatus, gas, bloating, cramp, diarrhea, and rarely vomiting), and amounts of lactose up to 12–24 g on a single occasion are tolerable by almost all people, no matter what their lactase status is (Lukito et al., 2015).

Reduced lactase activity causes primary lactose maldigestion, a condition that is occasionally asymptomatic. When symptoms are present, lactose intolerance is diagnosed. It is important to distinguish between primary hypolactasia and secondary causes of lactose maldigestion, including celiac disease, infectious enteritis, or Crohn’s disease, which have distinct pathogenic and therapeutic implications (Rasinperä et al., 2004). Moreover, primary hypolactasia should be distinguished from congenital lactase deficiency, a rare autosomal recessive disease with unique molecular mechanisms that affects infants from birth (Robayo-Torres and Nichols, 2007).

Lactose intolerance, a concept that emerged in the 1960s, privileges the European view of health and milk-rich Western diets that have been de facto universal reference points. The term frames the inability to digest milk after infancy as a defect—intolerance—when, in fact, it is the natural

state of more than two-thirds of the world's population, including most people in Asia. Young children almost universally produce lactase and can digest lactose in their mother's milk. As they mature, most switch off the lactase gene expression as children are weaned. Only about 35% of the human population can digest lactose beyond the age of about 7 or 8 (Leonardi et al., 2012).

There is evidence that genes play an important role in lactase persistence: some alleles have arisen in different populations worldwide, where the LCT gene plays an important role, and the variant LCT-13910C>T is completely associated with the lactase persistence phenotype and LCT-22018G>A is strongly associated. The gene LCT-13910C>T can usually be found in subjects of European descent (Mattar et al., 2012).

6.3.3 Fructose Intolerance

Fructose is a six-carbon monosaccharide sugar (hexose) that differs from glucose in that it has a ketone group (at carbon-2) instead of an aldehyde group (at carbon-1). It is also known as fruit sugar or laevulose. It is found as free sugar in fruits and honey, and as a constituent of disaccharide sucrose. It is 1.7 times as sweet as sucrose (Bender, 2009).

The pathophysiology of fructose malabsorption remains unclear, as Ebert and Witt (2016) show in their studies. If there are genetic or epigenetic variations in intestinal fructose transporters, such as GLUT5, GLUT2, or SGLT4, they need to be elucidated.

Since the absorption capacity for fructose is highly individual, it is difficult to determine the right dose for hydrogen breath tests (HBTs), which are the test normally used to diagnose fructose malabsorption. There is evidence that prevalence of fructose malabsorption correlates with age, and is higher at younger ages (Hoekstra et al., 1993). There is some agreement that 50 g of fructose in adults or 2 g/kg fructose in children exceeds the absorption capacity of the vast majority (Ebert and Witt, 2016).

Whether fructose malabsorption is more common in irritable bowel syndrome patients needs to be verified (Ebert and Witt, 2016). Hereditary fructose intolerance is caused by catalytic deficiency of aldolase B, a recessively inherited condition that affects homozygotes, to develop hypoglycemic and severe abdominal symptoms after eating foods that contain fructose and cognate sugars. Continued ingestion of noxious sugars leads to hepatic and renal injury, and also to growth retardation (Ali et al., 1998).

6.3.4 Histamine Intolerance

Biogenic amines are low-molecular-weight organic bases with biological activity that are formed in foods by either the microbial decarboxylation of the corresponding amino acids or the transamination of aldehydes and ketones by amino acid transaminases (Zhai et al., 2012).

Biogenic amines are universal regulators involved in the control of body homeostasis, and influence all vital body functions. They serve as transmitters for the central and peripheral nervous systems, and are also potent vasoactive agents. They influence blood supply to organs, act as hormones (adrenaline and noradrenaline), and influence gastric and intestinal ion secretion and intestinal motility (histamine and serotonin). Histamine is also a mediator of acute anaphylaxis and vascular permeability, and strongly influences immune responses (Beaven, 1970; Jutel et al., 2002).

Histamine is one of the most important of these amines, is formed by decarboxylation of the amino acid histidine in the body, and is also found in small amounts in foodstuffs, mainly in fermented products, cheeses, beer, chocolate, sauerkraut, and wines. The excessive release of histamine from mast cells is responsible for many symptoms of allergic reactions. It also stimulates gastric acid secretion (Bender, 2009).

Approximately 1% of the population has histamine intolerance, and 80% of these patients are middle-aged (Missbichler, 2004). In healthy persons, dietary histamine can be rapidly detoxified by amine oxidases crossing the intestinal epithelial barrier passively, whereas individuals with low amine oxidase activity are at risk of histamine toxicity. Diamine oxidase (DAO) is the main enzyme for the metabolism of ingested histamine (Maintz and Novak, 2007; Bodmer et al., 1999).

However, upon intake of high loads of biogenic amines with foods, this detoxification system is unable to eliminate biogenic amines sufficiently. A high histamine level can be considered from 5 mg/g (Rahimi et al., 2012; FDA, 2001).

Sensitive people to histamine present insufficient DAO activity (Bodmer et al., 1999). Besides DAO, monoamine oxidases (MAOs), distributed in different tissues of the human body, also participate in the physiological inactivation of biogenic amines (Bodmer et al., 1999).

Histamine has been identified by the FDA as a major chemical hazard of seafood products (FDA, 2001). Upon ingestion of food with a high histamine content, such as fish, cheese, meat products, and alcoholic beverages, histamine-intolerant patients have been described to suffer from a variety of symptoms, including gastrointestinal discomfort associated with vomiting or diarrhea, urticaria, rhinitis, headache, asthma-like symptoms, and cardiovascular complaints, such as hypotonia and tachycardia (Maintz and Novak, 2007; Amon et al., 1999).

6.4 Food Allergen Risk Management and Communication

Risks that arise from allergenic food can be viewed from the individual and societal public health perspectives. These two views are not identical; while

regulators and food manufacturers need to be mindful of the perspective of the allergic individual, their overall management of food allergy risks must be founded on a public health perspective (Madsen et al., 2010).

Knowledge to characterize the public health risk from allergenic foods is developing rapidly, as are methodologies to apply this knowledge to quantify risks more accurately (Madsen et al., 2009). A key finding is that the reactivity of allergic patients spans at least six orders of magnitude of allergen doses. One implication is that, in practice, it is often impossible within the constraints that apply to food production for normal consumption to guarantee that such foods will not provoke reactions in a few allergic individuals.

These findings also reinforce an emerging consensus that, as with other risks in society, a zero risk for food-allergic persons is not a realistic or attainable option. Scarcity of data and the reluctance to make decisions based on available data have led society worldwide to attempt to manage food allergy without setting science-based quantitative management thresholds. One consequence has been the lack of guidance to risk managers in both the public and food industries, which has led both groups to resort to individual judgments. As these judgments have not been shared, the application of the resulting risk management measures, such as precautionary labeling, lacks consistency and transparency. This lack of transparency not only creates uncertainty among food-allergic individuals, but also affects their quality of life. It also reduces public trust in food safety and leads to increased risk taking (Sampson et al., 2006; Greenhawt et al., 2009). Emerging data for, and new knowledge in, risk assessments offer the chance to develop quantitative limits on allergenic constituents present inadvertently in food products (management thresholds) and to thereby address these concerns. However, a prerequisite to their application is to admit an acceptable level of risk.

When the question arises as to why food allergy differs from other food hazards, it is important to state that toxic chemicals and infectious microorganisms in foods are generally hazardous for the whole population. There may be different levels of susceptibility (e.g., those who are ill, the very young, or elderly individuals may be more susceptible), but the overall population is at risk. In food allergy, only a minority of the population is at risk, and a food that is dangerous for the food-allergic person is often an important source of nutrients for the rest of the population.

Safety risks from toxic chemicals in the modern food and drinking water supply mostly concern the risk of chronic disease after prolonged exposure. For this type of exposure, those who may be affected are "theoretical" subjects with an increased probability of developing, for example, cancer. Manifestations of such effects are also often masked by a multitude of other influences on a person's health. In contrast, food allergens cause immediate reactions that can be fatal, and those affected are real, identifiable people with names, faces, and families.

Research has shown that if a risk is perceived to be inequitably distributed in society and causes damage to identifiable, rather than anonymous,

individuals, it is perceived as less acceptable (WHO, 2001). A perception that a risk cannot be controlled by those affected and can have severe consequences also reduces its acceptability. Therefore, a risk that arises from allergenic food is liable to be perceived as less acceptable—at least in allergic individuals—than the risk from many other food hazards, including those with acute manifestations, such as microbiological risks.

Eliminating all risks to food-allergic individuals from foods for normal consumption is unrealistic and unachievable, as already briefly discussed—hence the need to identify an acceptable level of risk. An acceptable level of risk might be defined as one at which the probability of an adverse event is minimized by taking into account the efficacy and feasibility of available risk reduction measures, and the nature and severity of the adverse effect and its impact on society at large.

To prevent adverse events, people with food allergies must diligently avoid allergenic foods, which depends on food safety controls all along the food production chain. Food allergen safety begins with producers and growers, and continues to include manufacturers, distributors, and transporters, as well as retailers, restaurants, and consumers themselves (Dupois et al., 2016). Food allergen guidance is provided in the Codex Alimentarius and is embedded in the principles of the HACCP Management System, which offer a prevention framework for the food industry globally (Codex Alimentarius, 2015; Wehr, 1997). In the United States, the FALCPA, passed in 2004, specifies that packaged foods must include labeling for eight of the common allergens identified by the Codex Alimentarius Committee on Food Labeling: wheat, crustacean shellfish, eggs, fish, peanuts, soy, milk, and tree nuts (Gendel and Zhu, 2013; Hey and Luedemann, 2001; Kjelkevik et al., 1997; Roses, 2011). For consumers with food allergies, trust in food processing, labeling, and handling is essential to manage their potentially life-threatening chronic condition.

Food consumed in restaurants or other food service settings accounted for approximately one in four food-induced anaphylaxis deaths between 1994 and 2006 (Bock et al., 2001, 2007). The role of restaurants in allergy management is particularly important since food allergy prevalence is on the rise (Branum and Lukacs, 2008) and American families are eating more meals at restaurants and preparing fewer meals at home. In the United States, 49.6% of all food dollars in 2013 were spent away from home (U.S. Department of Agriculture Economic Research Service, 2014a). Moreover, 20.8% of the food purchased away from home was procured at “limited-service eating places” (U.S. Department of Agriculture Economic Research Service, 2014b), where a customer orders food at a counter and does not receive table service (U.S. Department of Agriculture Economic Research Service, 2015).

Restaurant employees have critical roles to play in reducing the risk of food allergy adverse events. Their work requires specialized knowledge based on HACCP principles, as well as motivation to meet patrons’ needs, self-efficacy to employ best practices, and resources to execute safe food allergy

management protocols (Choi and Rajagopal, 2013; Muraro et al., 2014b). The preparation of a food allergy–safe meal begins even before a customer enters the restaurant, with steps that include careful review, segregation, and storage of ingredients (National Restaurant Association Educational Foundation, 2015b). Once a customer with food allergies enters a restaurant, a food service worker can employ a number of precautionary steps to mitigate risks, which include having a conversation with the customer to clarify food allergies, reading food labels, using uncontaminated ingredients, and delivering an allergen-free meal using properly sanitized service ware. Diversion at any point from best practices could have serious consequences for a highly allergic customer. While most states require some form of food safety training for restaurant workers, only five states and two cities—Massachusetts, Rhode Island, Michigan, New Jersey, Virginia, New York City, and St. Paul Minnesota—require additional food allergy training and/or food allergy materials to be displayed in restaurants (Abbot et al., 2007; Food Allergy Research and Education, 2015; Massachusetts Department of Public Health Bureau of Environmental Health/Food Protection Program, 2010; National Restaurant Association Educational Foundation, 2015a). Established training programs, like the National Restaurant Association's ServSafe Allergens Online Course (National Restaurant Association Educational Foundation, 2015b), describe the range of necessary and distinct steps to reduce the risk of food allergy adverse events in restaurants. Food service workers should be prepared to recognize and respond to food allergy adverse events when they actually occur. In the event of anaphylaxis, prompt administration of epinephrine is the preferred and lifesaving emergency response (Kemp et al., 2008), which should be followed by calling 9-1-1 and transporting the ill person to an emergency room (Muraro et al., 2014a; Sampson, 2003).

Across a broad range of food service environments (e.g., restaurants and institutions) and geographical areas (e.g., the United Kingdom, the United States, Malaysia, and Brazil), several studies have evaluated workers' food allergy knowledge by identifying potential hazards to food-allergic consumers (Ahuja and Sicherer, 2007; Ajala et al., 2010; Bailey et al., 2011; Choi and Rajagopal, 2013; Common et al., 2013; Shafie and Azman, 2015). These studies, which were conducted in select populations and convenience samples, have suggested the need for improved training and better adherence to HACCP practices and allergen management among food service workers. A study conducted in a small town in the United Kingdom reported that food service workers need additional training on food allergy management, and that proprietors and environmental health officers lack motivation, time, and money to invest in this issue (Pratten and Towers, 2003, 2004). Low levels of motivation and concern have also been reported by Ajala et al. (2010), who studied workers at 12 restaurants in Brazil. A study conducted at a university cafeteria in the United States revealed specific gaps in food allergy knowledge among food service workers, including challenges in identifying common food allergens among listed ingredients and lack of knowledge about

appropriate emergency response in the event of a severe food allergy reaction (Choi and Rajagopal, 2013). In Penang, Malaysia, food handlers were found to have moderate knowledge of safe food allergy management practices. For example, in that study, only about half of the respondents knew that eating even a small amount of an allergen could cause a reaction (Shafie and Azman, 2015). These studies provided important early documentation of potentially serious shortcomings in allergy management in food service establishments, and indicated the need for additional research that is generalizable to other settings.

Taking into account the consumers' perspective, advisory labels are helpful if they provide reliable information on allergen contents. However, manufacturers widely use them as a "safety net" to convey a nonspecified risk of possible contamination. An audit by the UK Anaphylaxis Campaign found that 69% of cereals and 56% of confectionery items were labeled as containing traces of nuts, despite none listing peanut or tree nuts as an ingredient (FSA, 2002).

Allergen labeling causes considerable anxiety for people with allergies and their carers (Cummings et al., 2010; FSA, 2002; Sheth et al., 2010). The format of labels varies considerably, and it is not uncommon for consumers to miss allergy warnings (FSA, 2002). Use of different expressions on advisory statements is confusing (FSA, 2002; Ng et al., 2011) and may contribute to the increasing trend for consumers to ignore them altogether (Barnett et al., 2011a; Hefle et al., 2007). A UK-based survey found that 60% of parents of children with nut allergies avoided products labeled "may contain traces," but only 40% did so when the statement was more vague, for example, "made in a factory that uses nuts" (Noimark et al., 2009). Similar findings have been reported elsewhere (Imamura et al., 2008), which suggests that the more ambiguous the warning, the less likely consumers are to heed content. However, no correlation has been found between the wording and the risk of cross-contamination (Crotty and Taylor, 2010; Hefle et al., 2007; Pele et al., 2007). Thus widespread use of poorly defined advisory labeling might paradoxically lead to increased risk taking. Do ambiguous labels contribute to the occurrence of allergic reactions? Published case series suggest that many food allergy reactions (including most deaths) happen outside the home after exposure to nonprepackaged foods, like those sold in catering establishments, which are currently exempt from allergen labeling legislation (Boden et al., 2005). However, few well-controlled studies have investigated this. A Canadian study found that labeling remains an important factor in unintentional exposure, with 47% of 651 allergic people attributing their reaction to a labeling-related issue (Sheth et al., 2010). In 29% of cases, the reaction was due to not reading the label correctly, while 8.3% were attributed to ignoring a precautionary statement.

The food industry is increasingly recognizing the role of labels in implementing preventive measures to protect allergic consumers from reactions through accidentally eating their problem food. However, it is also evident

that key knowledge and skills are essential to support them in undertaking effective food avoidance. In this context, the indiscriminate use of precautionary labeling has led allergic consumers to lose confidence in this risk communication tool (Crevel et al., 2014). In addition, the absence of such labels does not automatically imply that the given food is safe, as precautionary allergen labeling is voluntary. Therefore, appropriate communication strategies are needed (Barnett et al., 2011b), for example, communicating that reference doses, if available, are associated with a certain risk of reaction, and providing guidance according to standards. This, in turn, requires adequately training allergic patients to obtain relevant information on food products and from food suppliers. Therefore, the key element is close cooperation and effective communication among patient organizations, food industry representatives, and regulators. Moreover, adequate training of individuals who have contact with customers—from helpines, to those in the retailing and catering sectors, is of great importance. This also applies to those involved in caring for individuals with food allergies in the extended community, including personnel in day care centers and nurseries and teachers. This is all necessary to increase awareness about food allergies, and to thus reduce the risk of accidental exposure of food allergens, and to prompt action in the event of such exposure (Muraro et al., 2014a).

Finally, we cannot leave food from genetically modified organisms (GMOs) aside. One generally accepted belief is that genetically modified foods are directly linked with an increase in allergenic reactions, but no agreement on this point has been reached. Moreover, genetic engineering can be helpful to develop less allergenic foods.

Unlike foods from conventional organisms, whose consumption, from experience, appears safe, in the EU and many other countries, they may only be placed on the market when the organisms from which they were prepared have passed an authorization procedure with security checks. In the EU, the marketing of GMO and derived food and feed is controlled by Regulation (EC) 1829/2003.

In 1996, a task force of the International Food Biotechnology Council (IFBC) and the Allergy and Immunology Institute of the International Life Sciences Institute (ILSI) developed a decision tree approach to assess the potential allergenicity of the plants produced via agricultural biotechnology, where the source of the introduced novel gene or genes is a critical point (Metcalf et al., 1996).

Some studies have been carried out in the EU to determine differences in allergenicity between “natural” food and genetically modified food. This is the case of the study carried out by Niemann et al. (2016), which determined a very low impact on the overall assessment of inquiries, as there was only one case for which there was evidence for increased allergenicity of each genetically modified plant compared with the conventional baseline. It was a corn, possessing heat-tolerant alpha-amylase, which was composed of three genes of different strains of the bacteria of the genus *Thermococcales*.

Since the introduction of GMOs into the food chain has to be supervised by different health authorities, there is a risk of increased prevalence in food allergies, as these GMOs are limited.

6.5 Food Allergy Diagnosis

The evaluation requires a thorough history and physical examination to consider a broad differential diagnosis, to ascertain possible trigger foods, and to determine a likely general pathophysiological basis, specifically as to whether the food-induced allergic disorder is likely IgE mediated, which guides testing (Sicherer and Sampson, 2010). The history should determine the possible causal food or foods, the quantity ingested, the time course of the reaction, ancillary factors (exercise, aspirin, and alcohol), and the reaction consistency (American College of Allergy, Asthma, & Immunology, 2006). The history also focuses on details that might contribute to estimating the prior probability of an allergic reaction to a specific food. For example, reasoning dictates that a food ingested infrequently is more likely to be responsible for an acute reaction than one previously tolerated; contamination from a meal by a previously diagnosed allergen should be considered ahead of a less likely explanation, such as development of a new allergy to a previously tolerated food; major allergens are inherently more likely to be triggers than other foods. To reach a diagnosis, clinicians should consider the epidemiologic aspects of the disease (e.g., common triggers and common associations) and the details of the specific history, and then consider appropriate testing that can be evaluated in the context of these prior probability estimates (American College of Allergy, Asthma, & Immunology, 2006).

For IgE-mediated disorders, SPTs provide a rapid means to detect sensitization (American College of Allergy, Asthma, & Immunology, 2006). Negative SPT responses essentially confirm the absence of IgE-mediated allergic reactivity (negative predictive accuracy >90%). However, a positive test response does not necessarily prove that food is causal (specificity <100%). Consideration of a clinical history and disease pathophysiology is required to maximize the utility of test results. For example, a positive SPT response can be considered confirmatory when combined with a recent clear history of a food-induced allergic reaction to tested food. Additionally, increasing SPT wheal size correlates with an increasing likelihood of clinical allergy (American College of Allergy, Asthma, & Immunology, 2006; Knight et al., 2006). Studies have attempted to define wheal sizes above which an allergy is virtually confirmed based on the test result alone (Hill et al., 2004; Sporik et al., 2000). However, these studies have been limited to a few foods in infants and to using specific techniques in only a few populations (American College of Allergy, Asthma, & Immunology, 2006). One study

with 140 children evaluated peanut allergy; 64 had positive SPT responses, and 18 reacted during an oral peanut challenge (Pucar et al., 2001). Of the 17 children with an SPT wheal of more than 10 mm, only 8 reacted during the challenge. Thus, additional studies are needed to continue to define the diagnostic accuracy of skin test wheal sizes for different foods, ages, diseases, and populations; wheal size has not been correlated to severity of outcomes. When evaluating allergy to many fruits and vegetables, commercially prepared extracts are often inadequate because of the lability of the responsible allergen. Therefore, fresh food might be used for testing.

Serum immunoassays to determine food-specific IgE antibodies are another modality to evaluate IgE-mediated food allergy (Hamilton and Franklin, 2004). Increasingly higher concentrations of food-specific IgE levels correlate with an increasing likelihood of a clinical reaction, but do not generally correlate very well with reaction severity (Boyano-Martinez et al., 2002; Celik-Bilgili et al., 2005; Garcia-Ara et al., 2001; Osterballe and Bindslev-Jensen, 2003; Perry et al., 2004; Sampson, 2001).

Different predictive values are being generated from emerging studies, which might represent nuances of diet, age, disease, and challenge protocols (Osterballe and Bindslev-Jensen, 2003; Celik-Bilgili et al., 2005; Komata et al., 2007). Particular values associated with a high likelihood of clinical allergy (e.g., >95%) are often referred to as diagnostic values. Undetectable serum food-specific IgE might be associated with clinical reactions for 10%–25% (Roberts and Lack, 2005; Sampson, 2001). Consequently, if there is any suspicion of possible allergic reactivity, a negative SPT response or a negative physician-supervised food challenge result, or both, is necessary to confirm the absence of clinical allergy. Nomograms are available where prior probabilities can be used along with likelihood ratios (determined from studies that have evaluated the diagnostic utility of tests) to predict diagnosis. Yet very few studies have provided likelihood ratios, and results vary (American College of Allergy, Asthma, & Immunology, 2006). A drop in specific IgE concentrations is associated with an increasing chance of allergy resolution (Shek et al., 2004).

Despite not being commercially available, determination of specific IgE binding epitopes on an allergen might provide increased diagnostic utility (Cerecedo et al., 2008). The specific profiles of bound epitopes might reflect distinctions in binding to areas of an allergen that depend on protein folding (conformational epitopes), and are a feature of mild or transient allergy versus areas that represent stable linear binding regions, which reflect severe persistent allergy. Additionally, IgE responses to specific proteins in foods might account for particular outcomes (Steckelbroeck et al., 2008). For example, identification of IgE binding to labile birch pollen-related proteins is associated with mild reactions, whereas binding to stable lipid transfer proteins in the same foods is associated with more severe reactions. This observation forms the basis of an approach termed component-resolved diagnostics.

Increasingly, more studies are evaluating the utility of the atopy patch test for disorders in which symptoms are delayed after food ingestion, such as atopic dermatitis (Mehl et al., 2006), eosinophilic esophagitis (Spergel et al., 2007), and food protein-induced enterocolitis syndrome (Fogg et al., 2006). The test is run by placing foods under Finn chambers in a manner akin to testing for contact allergens. Although the atopy patch test is promising, there are currently no standardized reagents, methods of application, or interpretations, and additional diagnostic information in some studies appears marginal (Mehl et al., 2006; Spergel et al., 2007). Other future diagnostic modalities might include the basophil activation test (Wanich et al., 2009). Various tests and procedures (e.g., endoscopy or biopsy and hydrogen breath tests) might be required to evaluate possible gastrointestinal allergy (Furuta et al., 2007). Unproved or disproved tests such as pulse tests, applied kinesiology (muscle strength tests), cytotoxic tests, electrodermal tests, and immunoglobulin G (IgG) testing, should not be used (Bernstein et al., 2008).

The oral food challenge (OFC) comprises a gradual feeding of a possible allergen under medical supervision to determine tolerance or clinical reactivity. Severe reactions can be elicited; therefore, the procedure is undertaken by properly trained personnel with medications and equipment on hand to treat anaphylaxis. Feeding is generally stopped when objective or persistent subjective symptoms are elicited (Perry et al., 2004). For chronic disorders in which ingested food currently forms part of the diet, diagnosis typically includes a period to eliminate the possible trigger food or foods to determine whether symptoms resolve before an OFC. Caution is advised because acute severe reactions are sometimes noted after the reintroduction of a potential allergen (e.g., positive test result for IgE or suspicion of allergy) after prolonged dietary elimination (Flinterman et al., 2006). Open or single-blind OFCs are often used to screen for reactions. The double-blind, placebo-controlled OFC is the gold standard for diagnosing food allergies because bias is minimized (Bindeslev-Jensen et al., 2004). If the blinded challenge result is negative, it must be confirmed by open supervised feeding of a typical serving of food in its natural form to rule out a false-negative challenge result (approximately 1%–3%). Several reviews have outlined the procedures involved for OFCs (Bindeslev-Jensen et al., 2004; Bock et al., 1988), and a comprehensive clinically oriented guide has been published (Nowak-Wegrzyn et al., 2009).

6.5.1 Food Allergy Prevention

Data on primary prevention of food allergy through dietary means are limited, although numerous studies with various limitations have addressed outcomes of atopic disease, such as atopic dermatitis and asthma. Based on reviews in the available literature, professional organizations (Greer et al., 2008; Host et al., 2008) have generally concluded that there is insufficient

evidence for reduced atopic disease to recommend maternal avoidance of allergens during pregnancy or lactation. However, some evidence exists that allergen avoidance during lactation might be related to reducing atopic dermatitis. For infants with a family history of atopy, which places them at increased risk, data primarily support the practice of exclusive breast-feeding for at least 4 months, compared with feeding intact cow's milk formula, to decrease the cumulative incidence of atopic dermatitis and cow's milk allergy in the first 2 years. Similarly, avoidance of solid foods for the first 4–6 months is associated with a reduced risk of atopic dermatitis. For infants not being exclusively breast-fed, whole-protein formula (cow's milk or soy), compared with the use of extensively studied or partially hydrolyzed formulas, in the first few months of life appears to be associated with increased risks of atopic dermatitis. After 4–6 months, there are insufficient studies and data to suggest that specific allergen avoidance alters atopy outcomes.

6.5.2 Allergen Detection

To prevent contamination of the food chain by allergens, detection methods for allergens in foodstuffs have been developed. The challenge today is the detection and quantification of trace amounts of allergens in miscellaneous food matrixes, which are able to provoke an allergic reaction, with the severity depending on the allergen and the individual. The quantification of allergens in food first aims to guarantee with a high confidence level the absence of allergens in food for the allergic consumer. In parallel, the quantitative data obtained on patient serum can provide useful information about the allergenic potential of the food sample and the potential allergic reaction of the patient induced by ingestion of the foodstuff analyzed (Kirsch et al., 2009).

Among the available immunochemical methods, we first mention the most commonly used method in laboratories to detect hidden allergens in food, the enzyme-linked immunosorbent assay (ELISA). In an ELISA designed to screen allergenic proteins in food, antibodies mainly come from the serum of an immunized animal. This serum contains IgG, which is able to bind to the allergen used to immunize the animal, whereas in tests used for clinical diagnostics, the properties of IgE present in human serum are used. The food extract is analyzed in microplate wells. The principle of the quantification is based on the measurement of the enzymatic activity of a second protein-specific antibody (anti-IgG, e.g., a rabbit anti-human antibody) coupled to an enzyme. This second antibody binds to the allergen–primary antibody complex. The quantification can also be based on the measurement of the primary antibody bearing the enzyme label if any secondary antibody is used, as is the case in the direct ELISA. A reaction with the enzyme substrate produces a colored product, for which the absorption is proportional (direct, indirect, and sandwich ELISA) or inversely proportional (competitive ELISA) to the quantity of allergen in the food sample. A multiallergen immunoassay built from the ELISA model has been developed and allows

the simultaneous determination of at least 1 $\mu\text{g/g}$ protein of each peanut and tree nut allergen in chocolate, but a limit of quantitation has not been established yet (Ben Rejeb et al., 2005). ELISA has recently been combined with inductively coupled plasma mass spectrometry (ICP-MS) to increase the sensitivity and precision of the detection of a simple ELISA (Careri et al., 2007). In ELISA-ICP-MS, the secondary antibody is labeled with a stable isotope instead of an enzyme, and can be used for quantification with a mass spectrometer. As little as 2 μg of peanut allergens per gram of cereal-based matrix has been detected (Careri et al., 2007).

The polymerase chain reaction (PCR), a tool based on nucleic acids, has also been developed for the indirect analysis of allergenic ingredients in food. It involves targeting a segment of the gene coding for the allergenic protein of interest and amplifying only this deoxyribonucleic acid (DNA) fragment to make the protein detectable. This tool is highly specific and sensitive, having a lower limit of detection (LOD) of less than 10 mg/kg for almond, hazelnut, soy, milk, and peanut (Poms et al., 2004). PCR is also available as PCR coupled to ELISA and as real-time PCR. In PCR-ELISA, the detection is gel-free since the amplified DNA fragments are hybridized to a protein probe and detected by ELISA. In real-time PCR, the detection is gel-free and is performed in real time; amplification of the PCR product results in fluorescence proportional to the amount of the gene of interest in the food sample. There is the possibility to perform quantification using a unique internal standard to compensate for the variability in DNA extraction and amplification efficiencies (Hirao et al., 2006).

Regarding IgE-based methods, it is important to take into consideration that the IgE level in serum is very low (less than 1/40,000 IgG level) and a highly sensitive method is prerequisite for accurate diagnosis of allergy (Yunginger et al., 2000). Typically, the conventional *in vivo* testing method, including the SPT with allergens, is known to be sensitive and reliable. However, this method has a potential risk of causing adverse reactions, such as systemic reactions and anaphylactic shocks (Liccardi et al., 2006). In an effort to overcome the drawbacks of *in vivo* tests, *in vitro* serological analysis of allergen-specific IgE has been developed and employed, along with the *in vivo* provocation test for allergy diagnosis, especially when standardized allergen extracts are not available (Hamilton and Franklin, 2003; Hamilton and Franklin, 2004).

Since the radioallergosorbent test (RAST) (Wide et al., 1967) was reported in 1967, the original radioisotope assay in RAST has been replaced with the chromogenic enzyme immunoassay or fluorescent enzyme immunoassay (Fall et al., 2003). Currently, a commercialized CAP system is most widely used for the analysis of total IgEs and allergen-specific IgEs. Despite the availability of numerous *in vitro* methods for diagnosis of allergies, most of the assays are expensive and time-consuming, requiring large amounts of reagent and serum (Okochi et al., 1999).

In recent years, the use of magnetic microparticles has gained much attention in a micro total analysis system (μTAS) (Deng et al., 2001; Mirowski et

al., 2004; Pamme and Manz, 2004; Pamme, 2006). Due to their easy separation and conjugation with biomolecules (Safarik and Safarikova, 2002), magnetic microparticles have been widely used to develop various detection methods in microfluidic devices as a solid support for reactions (Hayes et al., 2001; Choi et al., 2002; Fan et al., 1999; Jiang and Harrison, 2000). Meanwhile, magnetic nanoparticles were employed as a label in a sandwich immunoassay of an analyte (Kriz et al., 1996, 2005; Graham et al., 2004; Enpuku et al., 1999). In this case, the amount of magnetic nanoparticles that are associated with a target analyte is proportional to the analyte concentration, and the signal generated from the magnetic nanoparticles can be used for quantitative analysis of a target analyte. For example, the superconducting quantum interference device (SQUID) and giant magnetoresistive (GMR) sensor have been attempted for immunoassays (Enpuku et al., 1999, 2003; Edelstein et al., 2000). The SQUID and GMR sensor generally allow a detection of analyte with high sensitivity, but these systems have some drawbacks, such as tedious washing steps, long analysis time, and cost of instrument. In addition, these methods have a serious limitation in multiplexed analysis and improvement of detection limits.

Alternatively, Hahn et al. (2007) have demonstrated the magnetophoretic immunoassay of mite allergen-specific human IgE in sera under an enhanced magnetic field gradient. The velocity of a magnetic nanoparticle-conjugated microbead was well correlated with the concentration of human IgE in serum. The developed system exhibited detection limits one order of magnitude lower than those of the conventional test kit (CAP system) for two types of mite allergens, showing good reliability. In addition, the magnetophoretic immunoassay system enabled a fast analysis with a smaller amount of reagents compared with the conventional method, supporting its utility for analysis of disease biomarkers, as well as specific allergens.

Finally, biosensors are considered an attractive alternative to traditional immunoassay methods offering comparable sensitivities and selectivity, while allowing for on-site detection (Turner, 2013). A number of studies have reported the use of biosensor-based quartz crystal microbalance (QCM), surface plasmon resonance (SPR), and electrochemical detection for the detection of milk protein allergens (Rebe Raz et al., 2010; Yman et al., 2006). SPR allows for the sensitive, on-line, and label-free detection of milk proteins. Several investigations have been done on the detection of milk allergens using SPR-based sensors. Haasnoot et al. (2004) developed a sensor for the detection of κ -casein with a detection limit of 0.1% or 100 $\mu\text{g/mL}$. Indyk and Filonzi (2005) and Muller-Renaud et al. (2005), designed biosensors against lactoferrin (LOD 19.9 $\mu\text{g/mL}$) and α -s1-casein (LOD 0.87 $\mu\text{g/mL}$), respectively (Indyk and Filonzi, 2005; Muller-Renaud et al., 2005). More recently, researchers have developed SPRi-based affinity tests to diagnose hypersensitivity (Chardin et al., 2014).

6.5.3 Future Therapies

Future therapeutic food allergy options include strategies that target specific foods and some that block allergic responses and are not food specific (Li, 2007; Nowak-Wegrzyn and Sicherer, 2008; Sicherer and Sampson, 2009). Of note, immunotherapeutic approaches are now being studied in an attempt to avoid serious adverse effects that would otherwise be triggered by the injection of native allergens. This has been noted in a study of injection immunotherapy for peanut allergy (Nelson et al., 1997) by changing the administration route or by modifying (engineering) treatment proteins. The approach that is currently being most investigated is oral immunotherapy (OIT), in which food protein doses are administered in gradually increasing amounts toward a maintenance dose. Jones et al. (2009) enrolled 39 children with peanut allergy in an open study of OIT. This study did not use initial OFCs, but after therapy for 4–22 months, and initially aimed for 300 mg as a maintenance dose; 27 of the 39 children completed the maintenance phase and tolerated the targeted 3.9 g of open peanut food challenge (18 had no symptoms). The immune parameters followed during the study revealed a decrease in skin test and basophil activation, a drop in peanut-specific IgE levels, and an increase in IgG levels (American College of Allergy, Asthma, & Immunology, 2006). In a first double-blind trial of milk OIT by Skripak et al. (2008), 19 children (12 completed active treatment and 7 received a placebo) underwent a regime of an initial escalation day (aiming for 50 mg), 8 weekly updosing to a final dose of 500 mg, and maintenance for 3–4 months. The median dose to elicit a reaction at the baseline was 40 mg, which increased to 5140 mg (range 2540–8140 mg) in the treated group, but remained unchanged in the placebo group. OIT is presumed to restore or induce a tolerant state. However, a distinction must be made between desensitization, in which the allergen is ingested without symptoms during treatment, but requires daily ingestion, and tolerance, in which food might be ingested without allergy symptoms despite abstinence periods. Studies to date have indicated that OIT induces desensitization, but it remains unclear whether tolerance is achieved (Buchanan et al., 2007). Staden et al. (2007) randomized children to egg or milk OIT ($n = 25$) or to observation during dietary elimination ($n = 20$); after OFCs at about 21 months on therapy, the treatment group discontinued daily therapy for 2 months and was rechallenged. Although 64% of the treatment group showed a good or at least partial response to OIT while on treatment, the food challenges performed 2 months off treatment revealed that only 36% continued to have true tolerance, a percentage that exactly matched the tolerance achieved in the untreated control subjects. More studies are required to assess safety (Hofmann et al., 2009), efficacy, and mechanisms.

6.6 Conclusion

Allergic consumers rely on the accessibility, accuracy, and quality of information on purchased food. For this reason, all parts in the food chain should enhance the control risk based on HACCP and other specific measures to avoid allergens in final products according to labels.

It has been well recognized that protecting allergic consumers from unintended exposure to allergenic food is a shared responsibility, in which each stakeholder must play its part: industries, EU authorities, consumers, and food handlers.

Finally, we should take into account that while substantial work has been done on detecting and measuring allergens in foods, very few studies on the prevalence and levels of undeclared allergens in a wide variety of foods are available.

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