

**An Update on Food Allergen Management
and Global Labeling Regulations**

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Dedication

I dedicate this thesis to
my father, Hongquan Diao
and my mother, Jun Liu
for their unconditional love and support.

Abstract

Food allergy is a growing concern worldwide, it has profound effects on the individual's quality of life, as well as a country's economy. There is an increasing recognition of food allergy pathogenesis, diagnostic methods and treatment therapies in recent years. Currently, food allergen management has been gradually established in different settings in order to reduce the occurrence of life-threatening food allergy reactions although the best practice to prevent food allergy is still strict avoidance. Food allergen labeling has proven to be an effective way to prevent accidentally access to potentially hazardous residues of the allergen for allergic consumers, however, inconsistency across countries regarding food allergen labeling legislation poses inconvenience in international food trade. Therefore, 3 topics will be discussed in this thesis (1) the current understanding of food allergy; (2) food allergen management in the industry, schools, restaurants and during/after pregnancy; (3) the status of food allergen labeling legislation around the world, including 164 countries which are current WTO members (till August 2017), an inventory was assembled and analyzed, future needs were identified by comparison.

Table of Contents

Chapter 1 Food Allergy Review	1
Food allergy definition.....	1
Food allergen classifications	4
Food allergy features.....	6
<i>High resistance to food processing</i>	6
<i>Cross-reactivity</i>	7
<i>Minimum eliciting dose and severity</i>	7
Epidemiological information.....	10
<i>Prevalence</i>	10
<i>Highly risk population</i>	12
Sensitization mechanism	13
Symptoms	16
Diagnosis	19
Treatment	22
New food allergenicity evaluation.....	27
Chapter 2 Food Allergen Management	28
Food allergen analytical methods	28
Food allergen management in the industry	30
Food allergen management in the restaurant	36
Food allergen management in the school.....	40
Maternity management	42
Chapter 3 Food Allergen Labeling around the World	43

Methodology: the search process	44
<i>The Codex Alimentarius</i>	45
Overview of national regulations	46
<i>Summary</i>	46
<i>African Region</i>	48
<i>Americas Region</i>	48
<i>East Asia region</i>	51
<i>Europe region</i>	51
<i>Eastern Mediterranean Region</i>	53
<i>Western Pacific Region</i>	53
Discussion	58
<i>What are “common allergens”</i>	60
<i>Whether the food allergen labeling voluntary or mandatory</i>	68
<i>Types of foodstuffs covered by food allergen labeling regulations</i>	69
<i>Exemption and addition</i>	70
<i>Ways indicating food allergens</i>	72
<i>Hidden ingredients and Precautionary allergen labeling</i>	73
Conclusion	78
Reference	79
Appendices	96
<i>Appendix 1. WHO Regional Map</i>	96
<i>Appendix 2. Member States</i>	97
<i>Appendix 3. Different methods of showing allergens on the labels</i>	98
<i>Appendix 4. Allergy Advisory Labelling Decision Tree assessment</i>	100

List of Tables

Table 1-1 Types of hypersensitivity2
Table 1-2 Different symptoms of food allergy 17
Table 1-3 Different types of treatments..... 26
Table 2-1 Examples of allergen management program documents 35
Table 2-2 Example of food allergen risk assessment form..... 38
Table 2-3 Tips to avoid cross-contact..... 39
Table 3-1 Summary of international food allergen labeling regulation status..... 47
Table 3-2 Food label related issues 58
Table 3-3 Examples of ingredient derived from milk..... 59
Table 3-4 Priority Allergens among Countries with Mandatory Allergen Labeling 63
Table 3-5 Examples of food groups in countries with mandatory food allergen labeling
..... 64
Table 3-6 Potential “hidden” source of food allergens..... 74
Table 3-7 Examples of Advisory Warning on Food Labels 75

List of Figures

Figure 1-1 Adverse reactions to foods.....2
Figure 1-2 Difference between Class I and Class II food allergen5
Figure 1-3 Mechanism of IgE-mediated allergic reactions 14
Figure 1-4 Traditional steps in diagnosing a food allergy 20
Figure 2-1 Allergen risk management in the industry and people involved..... 32

Chapter 1 Food Allergy Review

Food allergy definition

The definition of “food allergy” has been developed over time, a well-accepted food allergy definition is “adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food” as defined in the 2010 US National Institutes of Allergy and Infectious Diseases (NIAID)–sponsored guidelines [1]. This definition points out that food allergy is the type of hypersensitivity that has a proven immunological basis. Food allergy has often been confused with food intolerance. As shown in Figure 1-1, there are numerous adverse responses to foods, most of them are not the result of food allergies. Food allergy and food intolerance both belong to non-toxic adverse reactions to foods, food allergy is immune-mediated while food intolerance is non-immune mediated. The causes of food intolerance could be an enzymatic defect, the presence of the pharmacological substance or other undefined non-immunological triggers. The most common food intolerance is lactose malabsorption. Adults lacking beta-galactosidase in their small intestine can’t completely hydrolyze lactose into glucose and galactose, thus the incompletely hydrolyzed lactose reach the colon and be degraded by bacteria into H₂O, CO₂ and H₂. The fermentation in the colon causes different disturbances such as bloating, abdominal pain and sometimes diarrhea [2]. Other food additives, such as artificial flavors (e.g tartrazine) and food preservatives (e.g. sulfites) also can cause adverse reactions, but the mechanism is not well understood, for some patients, it involves immune responses, which can be recognized as a food allergy, for other patients, no immune response is identified, such reaction can be classified as food intolerance.

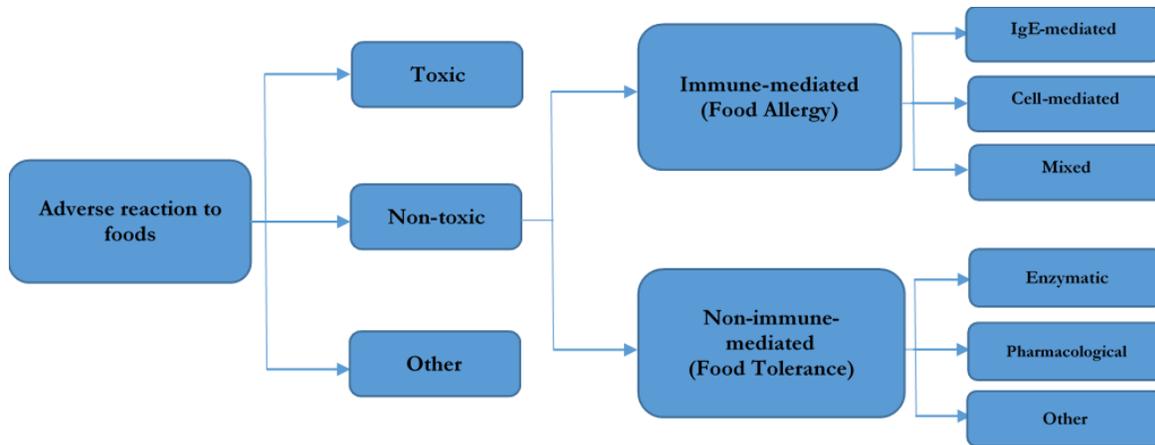


Figure 1-1 Adverse reactions to foods

The majority of food allergic reactions belong to Type I hypersensitivity, also known as IgE-mediated hypersensitivity. There are four forms of hypersensitivity (Table 1-1), besides Type I hypersensitivity, other three hypersensitivities involve immunological reactions, but are not mediated by IgE. To be specific, Type II hypersensitivity depends on antibodies such as IgG, IgM, and IgA; Type III hypersensitivity depends on immune complexes formed by antigens and antibodies; Type IV hypersensitivity refers to cell-mediated immunity [2]. For example, celiac disease is a disease often be wrongly assumed as

Type	Mechanism	Can foods induce this type of hypersensitivity	Examples
I	IgE	Yes	Egg/milk/peanut allergy
II	Cytotoxic	No	Autoimmune hemolytic anemia, Rh disease of the newborn
III	Immune complex	No	Systemic lupus erythematosus, farmer's lung
IV	Cell-mediated	Yes	Celiac disease, chronic food protein-induced enterocolitis syndrome

Table 1-1 Types of hypersensitivity

IgE-mediated food allergy, but in fact, it's a cell-mediated (Type IV) food allergy which means although it has an immunological component, it has a different etiology from the IgE-mediated allergy. The biggest difference between IgE mediated food allergy and cell-mediated food allergy is that IgE- mediated food allergy often cause immediate symptoms onset and the reactions can be more severe, while cell-mediated food allergy is primarily a chronic problem and does not cause immediate life-threatening reactions [3].

Food allergen classifications

According to Allergome database (www.allergome.org), 2477 allergen sources have been described as allergenic as of Jun 2, 2016. Most food allergens can cause reactions either in the raw or processed form. Two kinds of food allergens (Figure 1-2) have been distinguished according to their different immunologic mechanisms. Class I food allergens are most common and are primary sensitizers to allergic diseases, they can sensitize and elicit reactions in susceptible individuals, they are mainly water soluble glycol-proteins, the molecular weights are usually between 10-70kDa. Class I food allergens are stable to heat, acid and proteases, due to their particular resistance to gastric digestion, the sensitization process usually occurs in the gastrointestinal tract. Class II food allergens refer to the aeroallergens which can cause a variety of different symptoms in previously sensitized individuals by IgE cross-reactivity [4]. Currently, the diagnostic instrumentarium is satisfactory only for class I food allergens, since standardized extracts of Class II food allergens are difficult to isolate and highly labile [5][6].

Biologically, every protein has the potential to be allergenic, but it's not the case in reality. While some major allergens have been identified, for example, prolamins, cupins, profilins and Bet v1 accounts for 65% of all plant food allergens; ovomucoid in eggs, tropomyosin in Crustacea and mollusks; and casein in milk accounts for major allergens in the animal sources [7], but still, allergens come from proteins families with a wide range of biological functions and only a few biochemical characteristics can be associated with food allergen pathogenesis using current knowledge.

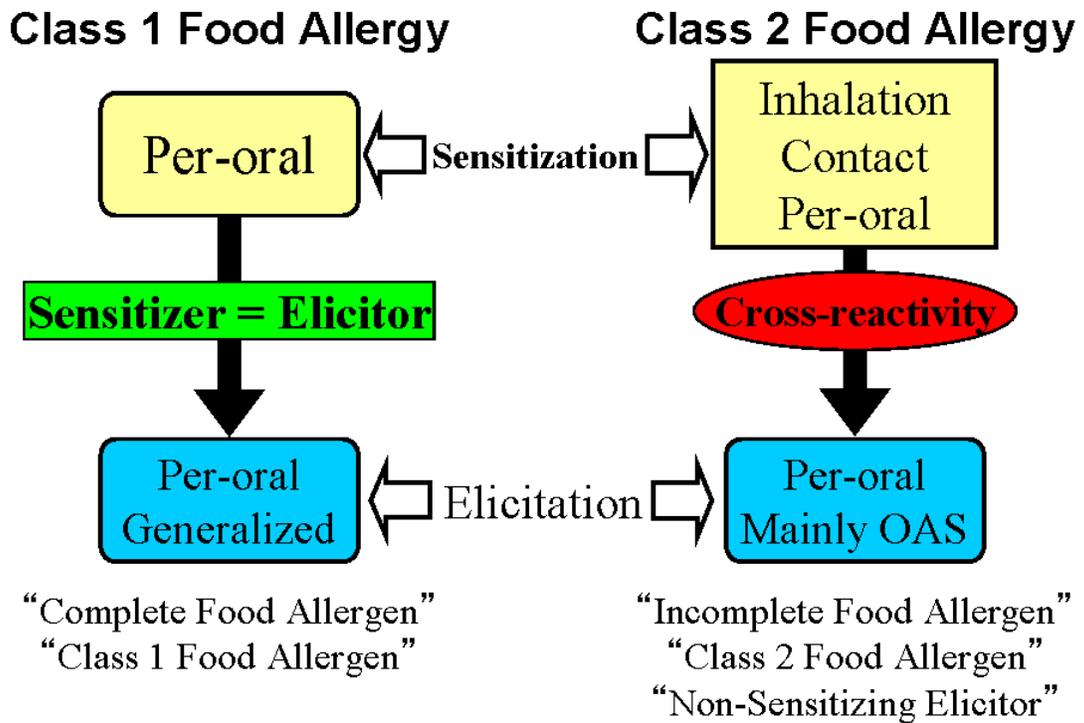


Figure 1-2 Difference between Class I and Class II food allergen

(Picture from <http://dmd.nihs.go.jp/latex/cross-e.html>)

Food allergy features

Theoretically, any protein would be capable of eliciting an allergic reaction, however, in reality, foods vary widely in their likelihood of provoking allergic sensitization. There are some studies trying to explain what makes certain protein more prone to be an allergen, the level of exposure and the properties of an allergen itself play important roles in determining the allergenicity potential [8, 9]. Obviously, a food protein that is abundant and resistant to digestion and processing has the higher potential to be allergenic, however, no universal conclusions have been made yet. For example, in cow's milk, most proteins are potential allergens even though some proteins present at a very low concentration [10]. Different conformational and linear epitopes widely spread all along the protein molecules, no specific structure nor function is associated with allergenicity of cow's milk proteins (CMPs). However, some sequential epitopes located in hydrophobic parts of the protein molecules have been proposed as good makers of persistent allergy to CMPs [10].

High resistance to food processing

Traditional or Class I food allergens, such as egg, milk proteins are heat-, enzymes-, and low pH-resistant. Other than allergens that cause oral allergen syndrome, food allergens which can reach gastrointestinal tract have molecular features that enhance stability to thermal and proteolytic denaturation.

Studies showed that some food allergens can maintain their allergenicity after roasting, high pressure, microwave, boiling, drying, High Intensity Interval Training (HIIT), high-voltage pulse and other commonly used high-strength food processing methods. For example, in Su et al's study[11], the allergenicity of several nuts(almonds, cashew, and walnuts) still remained after γ -irradiation in combination with different processing methods such as blanching, pressure cooking, oven roasting, frying, microwave heating. However,

most of the detection methods utilize in vitro methods such as Western blotting and enzyme-linked immunosorbent assay (ELISA), more accurate results on their allergenicity after processing in human subjects can be achieved by different Food Challenge tests.

Cross-reactivity

Cross-reactivity occurs when proteins from different food sources share a common antigenic determinant, in that case, the similar adverse reactions may be triggered by two or more different foods. According to the molecular basis of cross-reactivity, phylogenetically similar foods have better chance to cross-react with each other, however, a high degree of amino acid homology doesn't necessarily mean two protein will be cross-reactive. Studies showed that plant-derived foods are more likely to have cross-reactivity although individual sensitivity is also influenced by time and quantity. While cross-reactivity between different grasses highly correlates with their taxonomic classification [12], peanuts and tree nuts cross-reactivity cannot be safely predicted by their taxonomic relationships. Among tree nuts following botanical family associations, walnut (Juglandaceae), pecan (Juglandaceae) and hazelnut (Betulaceae) are strongly cross-reactive with each other, while the cross-reactivity of other nuts like hazelnuts, cashews, Brazil nuts, pistachios, and almonds are less pronounced. Peanuts as a major food allergen which belong to the family of Legumes, don't serologically cross-react with tree nuts [13], although there is controversy around whether there is a clinical association between peanuts and tree nut allergy [14,15,16].

Minimum eliciting dose and severity

A very distinctive pattern of food allergy is the unpredictability of the severity. There is a great individual variability in allergen threshold and no clear relationship between dose and severity is found. Studies showed that to the same offending food, individual threshold doses can vary from low milligram levels up to several grams. For example, when doing

Double Blind Placebo Controlled Food Challenge (DBPCF) with peanut-allergic patients, the individual threshold doses ranged from 2 to >50mg [17, 18], the similar variances also applied to other common food allergens such as egg, and cows' milk [19]. The variability and heterogeneity of the human responses suggest that different approaches should be used for individuals with same food allergy. Additionally, there is a positive correlation between doses of allergenic proteins and a cumulative presence of responses. Doses near the patient's individual threshold generally would provoke rather mild adverse reactions, however, some patients exposed to low levels of allergenic foods or proteins derived from allergenic foods would still experience noticeable adverse actions [20]. Clinically, there is also weak correlation between future adverse reactions and their severity of previous reactions, both similar and more severe reactions can be followed by a mild reaction [21, 22].

Given the long and growing list of high-risk foods, researchers are interested in determining the threshold levels of these problematic foods, above which the risk to food allergy sufferers is considered as being too high. However, clinical data for eliciting dose are still limited for most allergic foods except for most common food allergens like peanut, egg, and milk [23, 24]. Therefore, labeling regulations are not yet widely guided by threshold considerations.

In 2011, an expert panel was assembled to establish reference doses for 11 allergenic foods as part of the VITAL (Voluntary Incidental Trace Allergen Labeling) program [25]. In order to quantitatively assess the risk, researchers obtained individual no observed adverse effect levels (NOAELs) and lowest observed adverse effect levels (LOAELs) from low-dose oral clinical challenge studies with food-allergic individuals [26]. Within these 11 allergenic foods, the threshold ranged from 0.03 mg for egg protein (ED01) to 10 mg for shrimp protein

(ED05). The data were not significantly affected by the heterogeneity of the study methodology [25, 27].

Interestingly, people around the world have various attitudes towards knowing the fact that foods containing allergens that may cause no or mild reactions. Based on Marchisotto et al 's studies, they surveyed 16 countries around the world, mainly countries with established food allergen labeling regulations, the results showed that Japanese were most willing to accept the risk of potential reactions while Europeans were more restrictive [28]. This result may influence the manufactures' perspective on how to handle products with low risk of cross-contaminations with food allergens.

Epidemiological information

Prevalence

Accurate data on the prevalence of food allergy is unavailable, it has been estimated that around 1-2% of adults and 4-8% of children are affected by food-induced allergic disorders, the comparison between countries is hard to establish due to factors such as inconsistencies in study designs/methodologies and variations in the definition of food allergy. However, with increasing research being done in Asia, it is possible that the food allergy prevalence is similar around the world [29, 30, 31], which is contradict to the long-time belief that there are low prevalence rates of food allergy in Eastern countries than in Western countries [42]. Some studies revealed that, similar to Western countries, in Asia, milk and egg are the commonest triggers to food allergy, while soy, wheat, and peanut also account for many cases of food hypersensitivity [51]. Still, more information about the epidemiology and clinical spectrum of food allergy is needed in this area since Asian countries represent a large proportion of the world's population while the accountable prevalence date is limited in this area. Current obstacles of conducting research on food allergy in Asia are (1) most Asian countries are developing countries, their priority at this time is not food allergy research; (2) some Asian cuisines involve a lot of "hidden allergens" as they use different kinds of spices and contaminations are difficult to control; (3) data is often reported in local journals which are not accessible in conventional literature searches and difficult to understand without knowing certain languages and (4) some of the prevalence data is based on observation rather than scientific studies.

Although seems promising, it remains unclear whether the food allergy prevalence is increasing with current available data [32]. The epidemiological data may have been both under- and over-estimated of food allergy, since most data is collected via survey, the

intrinsic weakness of survey is people who respond to surveys are usually skewed towards populations that are more educated, affluent, and severely affected [28]. Moreover, self-reported food allergy is always higher in different studies represents a limited public awareness of food allergy and corresponding symptoms, respondents often confused the food allergy with other adverse food reactions [33].

The geographic variability of major allergens reflects a potential interaction of age, genetic factors, cultural and dietary habits (increasing ingestion of “junk foods”, fiber/prebiotics consumption) as well as time of first exposure to allergenic products [34], other factors including urbanization (“hygiene hypothesis”) [35], socioeconomic class [36], ethnicity [37], migration patterns [38], and medication (e.g. use of gastric acid suppressants and painkillers) have also been proposed to be related to the possible increasing prevalence of food allergy through observational research. Among all factors, age is the most important factor determining the type of food allergy, the most offending foods follow descending order for children are milk, egg, peanut, tree nuts, fish, and shellfish [39]; For adults, shellfish, peanuts, tree nuts and fish are the most common allergens [40, 41]. One reason that some foods are not typically showing allergenicity for children is late introduce of certain foods so that the data from longitudinal studies in childhood are unavailable. For example, shellfish will not be introduced early to children’s diet in a typical western-type diet [42]. Therefore, it’s very important for children with food allergy to re-evaluate their situation regularly.

One phenomenon needs to be aware of is that individuals may outgrow certain allergies with age. Generally speaking, younger children with milk or egg allergy may outgrow the allergy later in their lives. Whereas, tree nut, fish, and shellfish allergy may be last lifelong. For example, a study found 106 Korean children with atopic dermatitis and egg allergy diagnosed before 2 years old, 60% became tolerant to egg by age 5 [44]; A study from Spain reported that

more than half of children younger than 2 and allergic to egg became tolerant after 35 months [45]. Eighty-six percentage of children with IgE-mediated cow's milk allergy recovered at the age of 5, and in P. Meglio et al's [46] study, by introducing increasing daily doses of cow's milk, 71.4% infants can tolerant the daily intake of 200 mL milk during a 6-month period. It is suggested that is 6-12 months for younger children and 1-2 years for older children. For tree nut, fish and shellfish allergy, the evaluation may be performed every 2-4 years [43]. Clinically, a high initial food-specific IgE is associated with a lower rate of resolution in their late life, at the same time, if the food-specific IgE level decreases usually means the development of tolerance [47, 48]. Moreover, T cells also play a role in the development of tolerance. The ratio between T-regulatory cells and T helper 1 and 2 cells can also be predictors for food allergy outgrow [49]. Strict avoidance as a preventative method may be helpful in the process of outgrowing a food allergy [50], but contradictory theory (introducing allergenic foods in a young age) becomes increasingly popular these years.

Highly risk population

There are two groups of allergic people who are prone to have severe allergic reactions: infant and adolescent. Infants and children usually develop severe reactions when they contact to causative foods since it's hard for them to describe their needs and feelings.

Teenagers and those in their twenties, on the other hand, have limited awareness of food allergen risk and some adolescents even tend to intentionally consume known allergens under peer pressure and the rate of carrying the emergency medication devices are low, the feeling of isolation and presuming safe would bring adolescents in a risk situation [52].

According to Matthew et al [53], only 39.7% college students always avoided foods to which they were allergic, and only 6.6% reported always carried the device. Therefore, individuals die from a severe allergic reaction are often in this age group.

Sensitization mechanism

Most people have no adverse reactions to allergenic substances since human body has a defense system, when accessing to allergenic foods, most people can digest antigen into harmless substances, rather than eliciting an immune response. People who have immature or defective immune systems may have an allergic reaction, immunopathogenic of food allergy and the manifestation of various food allergic symptoms involves a complex interplay of genetics and environmental influence and still a lot remains unknown to scientists. Many studies have revealed the molecular mechanisms of food allergy, especially the IgE-mediated food allergy. Figure 1-3 showed a brief outline of the pathway of IgE-mediated food allergy sensitization. When the allergen substance is first introduced, a certain site(s) of allergenic proteins called “epitope” can induce allergen-specific IgE, IgE antibody can stay in the blood for 24-48h and the sensitized state will last for six months to a year without reintroducing the antigen. When an antigen enters the body again, IgE is quickly provoked and further bind to the high-affinity IgE receptors (FcεRI) posed on mast cells [54], basophils[55] as well as low-affinity receptors FcεRII (CD23) on platelets and eosinophil nuclei. After the formation of allergen-IgE-receptors complex, it can cause a series of biochemical changes and different kinds of mediators are secreted by degranulated mast cells or basophils (e.g. prostaglandins, cytokines, leukotrienes, histamine, slow reacting substance of anaphylaxis (SRS-A), heparin, platelet activation factor (PAF), eosinophil chemotactic factor of anaphylaxis, proteolytic enzymes) [56], these mediators then lead to various allergic symptoms. Both the presence of allergen-specific IgE and development of specific signs and symptoms are required for diagnosis of a food allergy since some individuals can develop allergen-specific IgE to causative foods without having clinical symptoms when exposed to food allergens [44].

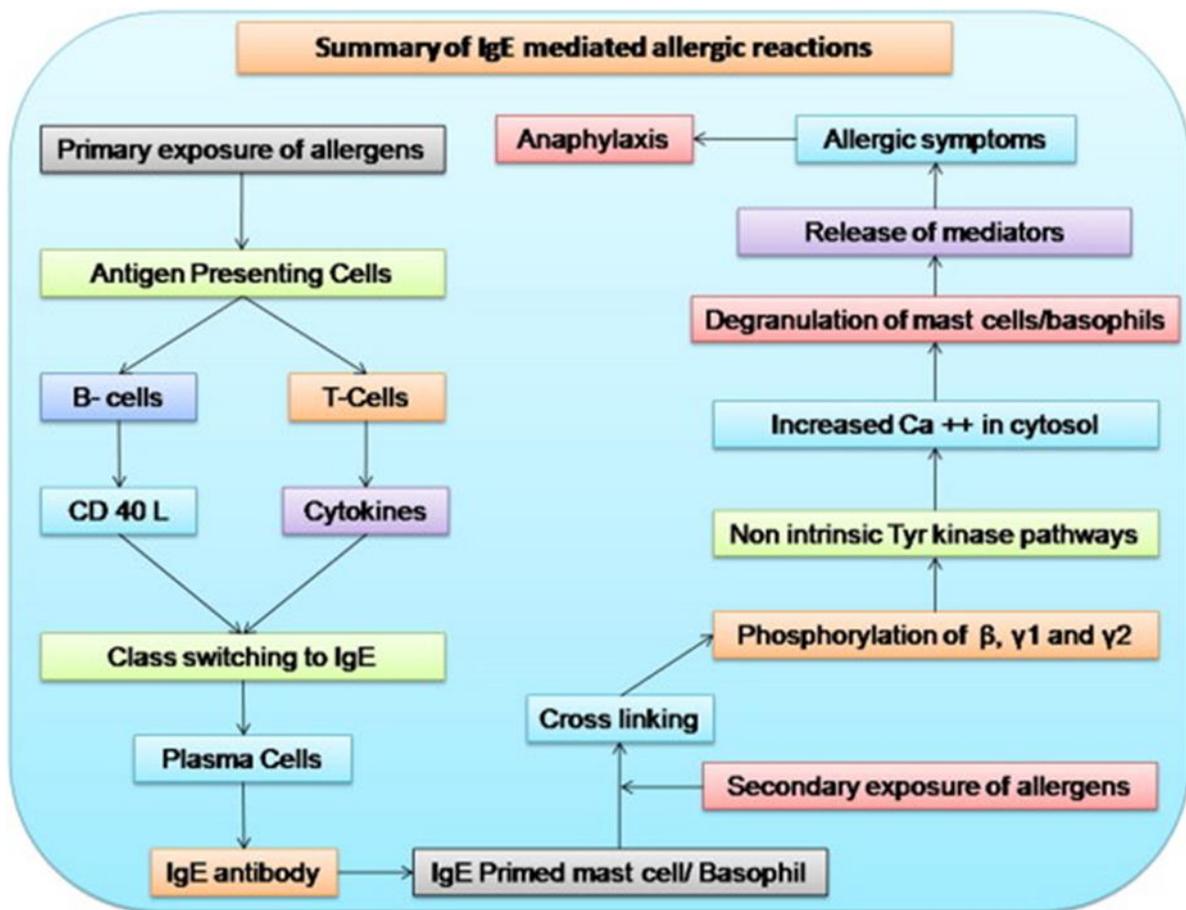


Figure 1-3 Mechanism of IgE-mediated allergic reactions

(Picture from <http://dmd.nihs.go.jp/latex/cross-e.html>)

Many good review papers [57-60] have discussed the roles and functions of each cell (e.g. antigen-presenting cells, T cells, humoral immune responses, homing receptors, signaling pathways), but still, many research is undergoing to fully understand cellular mechanisms of allergic sensitization.

The role of additional factors, also referred as co- or augmentation factors are known to intensify the severity of some food-allergic reactions. In 1979, Mauritz et al [61] reported a patient who developed anaphylactic symptoms only after jogging following shellfish consumption, this constellation was later be defined as “food-dependent exercise-induced anaphylaxis (FDEIA)”. Since then, co- factors such as physical exercise [62], non-steroidal

anti-inflammatory drugs (NSAID), alcohol [63], and acute infection [64] were discovered to increase the severity of food allergy. In many clinical cases, these factors are even obligatory to elicit symptoms of food allergy. The underlying mechanism is still undiscovered, but an increased absorption of allergens due to the gastroduodenal permeability has been believed as the possible mechanism for this type of anaphylaxis [65].

Some nutrients such as Vitamin D are also being suggested as co-factors in the development of IgE- mediated hypersensitivities to food. Vassallo et al [66] found there was a tendency that patients with food allergy are more often born in fall or winter, the seasonal differences in UV-B exposure and the fluctuations in Vitamin D were considered as the possible pathogenesis of food allergy. Vitamin D status as a risk factor for food allergy has not been fully investigated, several conflicting hypotheses that indicate both low and high Vitamin D levels have been correlated with allergic disease prevalence. Vitamin D has a number of known immunomodulatory effects that may contribute to develop immunologic tolerance and suppress pro-allergic immune responses [67, 68]. Other nutrients like dietary fat, antioxidants or individual health status such as being obesity, increased hygiene have also be associated with inducing food allergy, but most of the theories have not being scientifically validated [69].

Symptoms

Food allergy can cause symptoms ranging from barely perceptible discomfort to life-threatening anaphylactic shocks. There is individual variability of the food allergy clinical manifestations [2], risk factors associated with mortality include the quantity, timing, route of culprit food exposure, the food form (raw, cooked or processed) and patients' own situation (inflammatory states, body microbiota). Most people develop reactions by oral ingestion, some people develop allergic reactions after inhalation of airborne allergens or after cutaneous exposure. The primary target organs are skin, gastrointestinal tract, and respiratory system, Table 1-2 summarizes the various symptoms caused by food allergy. The most common cutaneous symptoms are urticaria (hives) and angioedema (swelling), both mucosal and skin exposure could induce contact urticarial, it should be noted that chronic urticaria is usually not associated with food allergy [70]. Vomiting, abdominal cramps, nausea, and diarrhea are frequently involved in gastrointestinal symptoms. Respiratory symptoms include persistent nasal congestion, persistent rhinorrhea, persistent sneezing, itching and tightness in the throat and nose, dysphonia, dyspnea, and/or wheezing [71, 72]. Symptoms such as itching or tingling are subjective, that's part of the reasons why perceived food allergy is always higher than the true prevalence [2, 73].

Recently, some scientists also mentioned emotional effects that food allergy may bring, some patients reported that they suffered from psychological distress which included anxiety, depression, agoraphobia, headache etc., because of their food allergy [74, 75], it may due to the culprit foods have some effects on patients' central nervous system, or patients indirectly suffer from food allergy due to the stress of coping with foods [76].

Organ	Symptoms
Skin	Itchy hives(90%), erythema, urticarial, angioedema, pruritus, burning sensation, eczema
Mucous membrane	Eye symptoms: Conjunctival hyperemia and edema pruritus, lacrimation, blepharedema Nasal symptoms: Rhinorrhea, nasal congestion, sneezing Oral symptoms: Discomfort/swelling of the oral cavity, lips or tongue (90%)
Respiratory organs	Discomfort/itch/tightness in the pharyngolarynx hoarseness, dysphagia, coughing, wheezing, retroactive breathing, feeling of chest tightness(70%), dyspnea, cyanosis
Digestive organs	Nausea, vomiting, abdominal pain, diarrhea(45%), hematochezia
Nerve	Headache, lowered vigor, unrest, impaired consciousness
Circulatory organs	Decreased blood pressure (45%), tachycardia, bradycardia, arrhythmia, coldness of limbs, pallor(peripheral circulatory failure)
Systemic	Anaphylaxis and anaphylactic shock

Table 1-2 Different symptoms of food allergy

However, making a comparison between different cases is difficult since psychosomatic reactions to foods varied from one individual to another. In fact, many patients believe that they are allergic or intolerant to certain foods, solely based on self-persuasion. Moreover, numerous unusual symptoms have also been ascribed to food allergies, such as aphthous ulcers, chronic nausea, lethargy, giddiness, sweating, food craving, general weakness, heatwaves, palpitations, blurred vision and a feeling of suffocation [77], the complexity of symptoms explains why some patients cannot be conclusively diagnosed whether they have a certain food allergy even following the most stringent clinical testing.

Food allergic reactions are often confined to one target organ, while they can cause one or more symptoms, in fact, food allergy symptoms are almost always associated with two or more clinical manifestations. In some cases, the complication of symptoms represents the severity of food allergy. For example, there are four severity levels of oral allergy syndrome (OAS), the syndrome usually involves symptoms like oral itching, lip swelling and laryngeal angioedema of the mouth and the pharynx upon contact with an allergenic food. The syndrome can become life-threatening to some patients when more organs involved and more symptoms triggered, however, while level 1 Oral Allergy Syndrome (OAS) occurred most common, the occurrence of level 2 is much rare compared to level 3 [2]. There is still no general agreement among clinicians regarding solid association between certain symptoms and culprit food, however, cow's milk was suggested to be avoided in children with gastrointestinal symptoms, whereas the majority of children (60%) with skin symptoms were required to exclude hen's egg [78].

Diagnosis

There are several methods for identifying hypothesized food allergen on human subjects. The mechanism is to (1) detect specific IgE (2) detect specific symptoms on patients when introducing the suspected allergy source. Figure 1-4 shows the common steps in diagnosing food allergy. Suspected allergy source can be used either as raw foods or be processed into another format according to experiment conditions [79], to be noted, the diagnostic accuracy of specific IgE varies with the format of testing foods [80]. In order to stimulate the real situation, raw food is preferred in clinical in vivo tests (e.g. skin prick test) since thermal processing commercial extracts may alter the allergenicity of suspected foods [81]. The diagnosis of food allergy begins with a comprehensive history taking, a detailed diet history can aid in limiting the choices of allergens to be tested. Information obtained often include (1) type, quantity, time of food taking; (2) time interval between food ingestion and symptoms onset; (3) additional factors [82]. The main weakness of clinical histories is that it may involve human bias, the accuracy can be improved by different types of food challenge studies (double-blind, placebo-controlled food challenge (DBPCFC), single-blind food challenge, and open-food challenge) [77]. When suspected allergens are determined, an incremental oral food challenge is followed to validate the hypothesis. Double-blind, placebo-controlled food challenge (DBPCFC) is widely used, it has been called the “gold standard” for food allergy diagnosis and believed to be the only conclusive experiment for food allergy by European Academy of Allergy and Clinical Immunology (EAACI) [83, 84]. Other tests like skin prick testing (SPT), the radioallergosorbent test (RAST), histamine detection, passive transfer test and human serologic studies also been used for the diagnosis

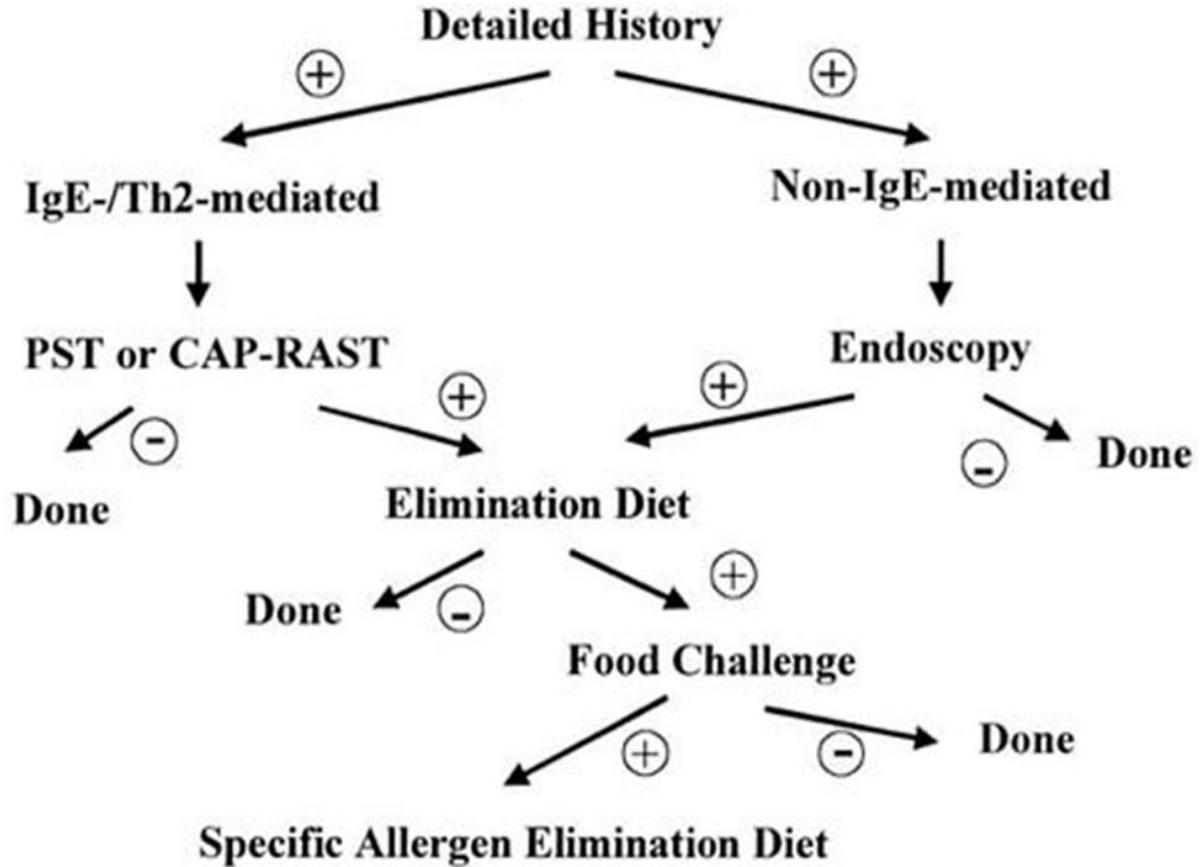


Figure 1-4 Traditional steps in diagnosing a food allergy [106]

of Type I hypersensitivity reactions. The mechanism of SPT and RAST is to measure the allergen-specific IgE indirectly or directly, the results may provide an indication of the likelihood of food allergy, however, in some cases, there is no or weak correlation between SPT results and the quantity of allergen-specific IgE. In Hourihanea et al’s study, there is no apparent correlation between the mean diameter of SPT wheal and peanut-specific IgE concentration in patients [20]. Moreover, positive SPT or RAST alone does not substantiate the diagnosis of a food allergy since the presence of IgE is not necessary lead to allergic reactions when exposure to food allergens [85]. Furthermore, 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 [20, 87, 88]. Despite all these defects, SPT and RAST are still the most common methods for diagnosing the food allergy, SPT is suggested to be more reliable than RAST since RAST depends on serum IgE, which has a short half-life in the circulation [63]. Therefore, data from more than one test systems are believed to provide more accurate diagnosis since different testing methods involve varying aspects of the human immunologic response to food antigens and sometimes providing different results.

Misdiagnosis leads to the increased economic burden on both the food allergy subjects and the health care system. It is reported that food allergy panel testing often results in misdiagnosis of food allergy [89]. Some promising novel diagnostic approaches were developed recently, such as molecular or component-resolved diagnostic tests (CRD) and Basophil activation tests (BATs), by measuring sIgE antibodies for major allergen proteins, CRD showed the potential to improve the specificity and sensitivity of testing peanut food allergy. BATs have shown higher specificity while maintain sensitivity compared to SPT and CRD, however, the use of these two tests are still limited since more well-designed studies needed to be done in order to assess the diagnostic value of these tests [90].

Treatment

There are generally three basic phenotypes of food allergy: transient food allergy, persistent food allergy, and food-pollen (oral allergy) syndrome [93]. Different immunotherapeutic approaches are suggested to deal with different food allergy. The ideal therapy should help patients develop tolerance while having short treatment course and doesn't develop serious side-effects during the therapy.

When the acute onset of severe food allergy reactions or anaphylaxis happens, proper use of epinephrine can save patients' lives. In some cases, injecting epinephrine at the time of first symptoms occurrence is recommended; If previous anaphylaxis with cardiovascular collapse occurred, it's advisable to inject before symptoms occur [94]. Pediatricians should introduce right ways to use autoinjectors, while it's also important that patients (or caregivers) need to properly store and periodically review and update their devices.

Currently, the best treatment for food allergic subjects is strict avoidance of the causative foods. However, avoidance of allergenic foods can limit food choices for patients especially when substances are widely used as everyday staples such as eggs and milk, which may possibly create nutritional deficiency [95] and psychological burden for food allergy patients and their families [96]. Although it's clinically rare to find patients who can't maintain nutrition due to their multiple food allergies, it may still be a potential threat for food allergy patients especially for children within the first 2 years of life, at this period, the growth velocity is particularly rapid while the prevalence of food allergy is also high. Lacking protein and other nutrients during this period may have unfavorable effects on children's later life. Many studies have been conducted on the effect of food elimination diets to children's health. In Meyer et al's studies [75], they found that 8.5% of all allergic

children enrolled were underweight, while 11.5% of all children enrolled had low height for their age (≤ -2 Z-score classified by the WHO), however, obesity has also been seen in the same study and they didn't find particular association between certain food allergy and unusual growth rate. Although single anthropometric measures cannot accurately indicate growth and some exceptions may exist, the results still highlighted that children with food allergies are more likely to be underweight than the general UK population. Moreover, since the symptoms vary and lacking determining testing methods, self-diagnose and inappropriate tests may lead to misdiagnosis of food allergy, an overly restrictive elimination diet may bring severe consequences on children's growth [28].

Due to the inconvenience of passive avoidance, researchers are trying to develop some active ways for curing food allergy or significantly lower the threshold of provoking doses for food allergy. Treatments like allergen-specific immunotherapy and medicine have been developed over the past few years, most attention has been given to allergens which can trigger severe food allergy such as egg, milk and peanuts [97]. There are mainly three types of treatments which involve different kinds of mechanisms and have both advantages and disadvantages (Table 1-3). The ultimate goal of immunotherapy is to cure food allergy, resulting in permanent tolerance, but to many patients, desensitization, which means increasing the doses of allergen needed to trigger the allergic reactions are also a desirable results of therapies. The first type of immunotherapy is based on the concept that gradually increasing the quantity of antigen exposure to oral mucosa and the gut-associated lymphoid system will lead to tolerance. Oral immunotherapy (OIT), sublingual immunotherapy (SLIT), and epicutaneous immunotherapy (EPIT) are three promising clinical treatments that have been tested for the food allergy desensitization [98]. With these treatments, patients are first

given minute amounts of allergen orally in a controlled clinical setting, the quantity is increased over a course of time. Although OIT and SLIT for egg, milk, and hazelnut appear to provide desensitization during therapy, long-term results are not being identified [99]. An alternative approach to food OIT is using extensively heated (baked) milk and egg, this treatment method has already shown effectiveness in some clinical trials [100]. Regarding the multi-food OIT, in Bégin's [101] study, the result has shown that multi-food OIT is not inherently riskier than single-food OIT, but the further study is still needed to fully investigate the efficiency and safety of multi-food OIT.

The second type of therapy is based on the idea to prevent the molecular interactions during the sensitization process by using different biological agents targeting specific mediators of an allergic reaction [102]. One promising therapy is peptide immunotherapy (PIT), PIT harnesses the body's capacity to induce peripheral T cell tolerance, the mast cells are not activated since peptides are less likely to cross-link IgE molecules [103, 104]. Another method is Plasmid DNA-encoded vaccines, immunization with bacterial plasmid DNA (pDNA) that encodes specific antigens can induce prolonged humoral and cellular immune Th1 responses. However, this approach has only been tested in the animal models and shown to be strain-relevant [105]. As allergen-nonspecific therapy, anti-IgE therapy showed promising results in increasing the threshold of peanut allergy in a multicenter clinical trial, but the effectiveness was not universal [93].

The third type referred to therapies which have mechanism that are not fully understood. Julie Wang et al [71] has developed a Food Allergy Herbal Formula-2 (FAHF-2) based on traditional Chinese medicine, although it showed efficacy in a murine model, no

efficacy was demonstrated at the dose and duration used in the testing trials on human subjects.

Although some therapies are promising, all the treatments mentioned above are still far from being routinely used before full efficacy assessments and safety evaluation be addressed [107]. Among the plethora of novel approaches, most of them are still in an animal model testing stage, the next step is to select the most promising strategies and apply them on human subjects, such as the Chinese herbal formula FAHF-2 and OIT alone or in combination with the anti-IgE antibody. It will also be interesting to see whether additional routes, such as lymphatic immunotherapy, become viable for food immunotherapy [108].

Fundamental idea	Therapy	Immune rational	Benefits	Risk	Status
Gradual increasing antigen presentation in nonmucosal might induce tolerance	Subcutaneous immunotherapy(SCIT)		Proved efficacy and safety in the treatment for aeroallergens	Systemic allergic reaction may occur	Clinical
	Sublingual/OIT		Natural foods, reduced risk of systemic anaphylaxis compared with injections	Resolution of allergy without ongoing treatment is not achieved	Clinical
Interface cellular interaction	Recombinant vaccines	Reduced IgE activation by mutation of IgE-binding epitopes	A safer form of immunotherapy compared with injection of native protein	Require identification of IgE binding sites for each allergen	Preclinical and clinical
	Peptide vaccine (overlapping peptides)	Peptides are less likely to cross-link IgE, avoid mast cell activation	No requirement for IgE epitope mapping/mutation	Require identification of T cell epitopes for each allergen	Preclinical
	Plasmid DNA-encoded vaccines	Endogenous production of allergen might result in tolerance	Possible 1-dose treatment	Studies on mice showed strong strain-dependent effects	Preclinical
	Anti-IgE antibodies	Targeted toward Fc portion of antibody, can inactivating mast cells	Not food specific, some response in eosinophilic gastro enteropathy (pilot study)	Side effects are common	Clinical
Mechanism unknown	Chinese Herbal medicine		Not food specific		Preclinical

Table 1-3 Different types of treatments [97]

New food allergenicity evaluation

Nowadays, manufacturers are consistently bringing new ingredients to the market in order to satisfy consumers' desire for new foods. The introduction of new food proteins may bring the risk of new food allergens. Reliable experimental methods haven't been established for testing new protein allergenicity. The first embodiment is the Decision-tree Evaluation Structure for evaluating genetically modified food allergens immunogenicity created by International Food Biotechnology Council and the Allergy and Immunology Institute of the International Life Sciences Institute (I F B C / I L S I) in 1996 [91]. In 2001, WHO/FAO adopted I F B C / I L S I evaluation structure and made a comprehensive revision. They again used a tree evaluation model to assess each allergen properties from amino acids sequence homology to protein structural similarity, the allergenicity will also be verified by in vitro testing using patients' serum with known allergens. Additional assessments of the potential allergenicity testing pepsin resistance and using animal models will also be performed in order to get comprehensive results. New foods derived from biotechnology can be assessed as safe only when receiving all negative results through all the evaluations [92].

Chapter 2 Food Allergen Management

Allergenic foods have been identified as a food safety hazard and may affect millions of consumers if not properly controlled. The civil rights of patients with severe food allergies have not been widely a concern of the regulators [109], however, children with life-threatening food allergies are considered disabled under federal civil rights laws in the U.S. and are protected accordingly. With the increasing knowledge about biological and clinical characteristics of food allergy, collective efforts from the food industry, governments, clinicians and food scientists have been made to protect sensitive consumers. The concept of food allergen management was first introduced around last decade of 20th century and has been widely accepted over the last 20 years [110], divergent practices in allergen management have been applied by different authorities, which will be briefly discussed in this chapter.

Food allergen analytical methods

Without effective treatments, rapid and simple detection methods are desired for allergic patients and food providers for prevention. An effective method should have excellent specificity as well as sensitivity because a great variety of food components can interfere with the assay, while to some people, even a low dose can cause severe reactions. In the current stage, there are several analytical methods existing for the quantitative and qualitative detection of allergenic residues in foods, most detection methods are immunoassays, which utilize antibodies raised against the target food or food protein extracts, this may lead to the underestimate of the risk of allergenic food proteins since the exact

epitopes would be changed or masked during processing. Meanwhile, cross-reactivity between allergenic food proteins can result in false positives in protein-based assays.

The most commonly employed detection methods in the industry include linked immunosorbent assays (ELISAs), polymerase chain reaction (PCR) and mass spectrometry, these methods are currently available commercially for detecting residues from allergenic sources [7]. Enzyme-linked immunosorbent assays (ELISAs) have been the most favored analytical method used by the food industry and regulatory agencies to monitor the allergen residues for their relatively satisfactory sensitivity and specificity, but a significant drawback is that this method is very laborious and time-consuming. With continuous development and improvement, lateral flow device (LFD) is one of the most widely used ELISA platforms applied by the food industry today which allows rapid determination of allergen residue. As food allergy becomes a global challenge which has a great impact on quality of life of patients, quick, cheap, reliable biosensor techniques are demanded to better protect sensitive individuals, surface plasmon resonance (SPR) is a promising technique in the food allergen detection field, using biosensor techniques, SPR is capable of detecting even trace amount of food allergens without complex sample preparation [7]. Moreover, SPR is also a labor-free detecting method in which the binding event can be monitored in real-time. Other new technologies like microfluidic device [111] and optical thin film biochips [112] have also been introduced as novel detection methods, but further assessments to validate their productivity in the real world is still lacking.

Some countries such as U.S, EU and Japan [112, 59, 41] have published guidance on validated food allergen detection methods for most major common allergenic foods, however, except test methods listed in Japanese legislation and Codex (R5 Mendez test for gluten-free

foods), most country do not have recognized standard food allergen test methods, there is still in a working process to develop assays to cover all major food allergens listed in different regulations. Novel food allergen detection methods should be accurate, robust, comparable, easy-interpret regardless the variability in sampling, food matrix extraction, methods could be considered routinely applied in allergen risk management process when aforementioned criteria are met.

Food allergen management in the industry

In order to minimize the risk for sensitive people from accidentally consuming allergenic ingredients, while providing a wide choice of products, manufacturers are encouraged to establish an effective food allergen control program. The primary objectives of the allergen control plan are to ensure (1) products containing allergens are properly labeled, otherwise (2) no products contain undeclared allergens. However, at the current stage, universal allergen control approaches and standards are non-exist, individual manufacturer takes different measures to deal with the risk in their supply chains. Most of the countries around the world have food laws which set some basic requirements for food safety management. For example, The *Federal Food, Drug, and Cosmetic Act (FFDCA)* (<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCA/default.htm>) is the principal food law of the United States. It states that food should not be adulterated. In order to comply with these fundamental requirements, the U.S Food and Drug Administration (FDA) promulgated good manufacturing practices (GMPs) in 1969 to establish some specific criteria for compliance, GMPs has further being reviewed and updated as current good manufacturing practices (cGMPs). Food allergen management

program depends on requirements of cGMPs and in return cGMPs simplify the development and maintain process of a specific food allergen management program [113]. How well the allergen control program helps to reduce the allergen risk in the industry depends on a combination of factors such as the nature of the allergen, employee practices and the quality of other support programs. Some obstacles could be (1) most employees in the food company have limited knowledge about food allergy (2) company always choose to use the most cost-efficient way rather than the best way when dealing with the problem (3) individual's resolution plan for the emergency may contradict to the established best practice. Still, adequate control can be achieved through proper training, diligent adherence to the procedures, and reliable supervision.

- Allergen management team

Assembling a highly responsible allergen management team is the essential and foremost step in developing a successful allergen control plan (Figure 2-1). The team will develop procedures and requirements in accordance with the company's allergen control policies and objectives, they need to evaluate and identify the safety hazards associated with possible food allergens and then use various means to decrease the safety risks.

- Product/Facility/Production Design

When designing a new plant or launching a new product, designers should incorporate features to minimize the potential cross-contact of allergens.

Product- only adding allergenic ingredients to new products when they make a real difference in taste or functionality.

Facility- Purchasing the equipment that can prevent the accumulation of food residue and easy for cleaning and inspection.

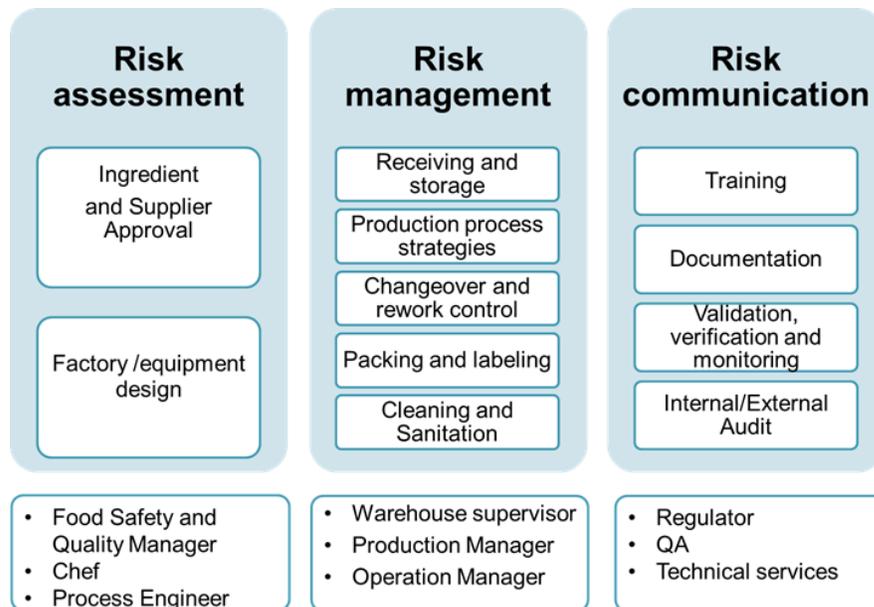


Figure 2-1 Allergen risk management in the industry and people involved

Production

- Design the movement routes of materials and personnel traffic in order to prevent cross-contact, sometimes, physical barrier and warning sign can be applied so as allergenic ingredients can be limited to certain areas of the plant.
- Dedicate lines and equipment for the production of allergen-containing products
- Control the daily scheduling and specify the order of addition of allergen ingredients so as to limit the potential of cross-contact of non-allergen containing foods with allergenic ingredients during the processing. In general, allergenic ingredients are suggested to be added later than earlier during the processing.
- Allergen changeover. Proper cleaning methods need to be utilized during changeover from allergen-containing foods to non-allergen containing foods; surrounding equipment should be protected; moreover, extending operating hours of an allergen –containing run will help to reduce the number of required changeovers.

- Supplier Control

It's important for companies to maintain a trustworthy and transparent relationship with suppliers in order to ensure raw ingredients or processing aids are "safe" when entering facilities. Companies should first verify supplier having accepted allergen control programs and audit records. "Supplier survey" is a good tool for companies to determine the risk associated with material they are receiving [113], when vendor is approved, individual ingredient should also be approved to use in the facility in a case-by-case basis by the food safety and quality department.

- Ingredients receiving, handling and storage

Receiving personnel are responsible for inspecting all ingredients and other materials to make sure they carry correct labels and do not have the opportunity for cross-contamination (e.g. broken package). Moreover, the delivery vehicle's cargo area should be inspected after unloading. After proper receipt of the allergens and allergen-containing ingredients, transportation and storage of these ingredients within the facility need to minimize the risk of cross-contact: store allergenic ingredients and non-allergenic ingredients in different areas or store allergenic ingredients below non-allergenic ingredients when the storage area is limited. A color-coded system is widely used by different facilities to assure potential risks are visibly marked and easily differentiate from normal ingredients. The exact procedures will depend upon the nature of certain food allergens and the structure and space of the facility, proper procedures should be documented as a standard operating procedure (SOP) for employees to follow. For some allergens, dust generation during handling of allergen-containing items can be a problem; in that case, valid allergen testing methods can be employed to determine if the spread of allergenic dust presents a hazard [114].

- Re-work

Proper labels should be provided in order to prevent accidental use of an allergen-containing material in a non-allergen-containing product during rework. It's advisable to follow the "Like-into-like" or "Exact-into-exact" practices when introducing the allergen-containing materials. For example, peanut-containing ice cream must not be added to ice cream that does not contain peanut. Also, an informative document should be kept for further reference.

- Cleaning and Sanitation

A company's cleaning and sanitation program plays a vital role in food allergen management, effective cleaning and sanitation will remove product residues to an accepted level. "Wet cleaning" and "Dry clean" are chosen based upon the nature of product produced. Wet cleaning is preferred since allergic protein tends to be soluble in hot water. It's reported that if manufacturers used hot water to clean their equipment, the content of allergen has the possibility not to induce a severe allergic reaction [115]. Proper validation methods need to be applied in order to prove the effectiveness of cleaning and sanitation methods, this is often being done with some allergen test kits. The actual validation process should include a physical validation (personal check) of all accessible direct and indirect food contact surfaces, then appropriate quantitative analytical tests such as enzyme-linked immunosorbent assay (ELISA) can be performed.

- Documentation

A well-documented food allergen program (Table 2-1) will help to achieve the specific safety goals. Written procedures (e.g. sanitation standard operating procedures (SSOPs), standard operating procedures (SOPs), monitoring, corrective action and verification activities) that are

relevant, detailed, and easy to understand will most likely to assist employees to understand and comply with the program. At the same time, employees should maintain good records in a timely and accurate manner in order to show procedures are being followed properly, the written records are also very important for verification activities.

Identify hazard	Detailed product recipe/formula Specification of each ingredient Investigate production flow for potential cross contact issues
Management procedure	Detailed written SOP and SSOPs for each production process Monitoring/corrective action and verification practices records
Supporting documents	The reasoning behind each control activity Supplier/ingredient approval record , documents need to be renewed in a regular basis Allergen training materials/records

Table 2-1 Examples of allergen management program documents

- Labeling

Manufacturers should properly implement the food allergen management program in order to protect the allergic consumer. An informative and well-designed the label will help to prevent allergic consumers from accidentally consuming allergens. As incorrect labeling is the main cause of allergy-related product recalls, it’s essential for manufactures to establish procedures to check the labels as to minimize any potential cross-packing. Employees responsible for packaging should pay special attention during product changeover, a simple check-list may often be effective [113], more “high-tech” options such as bar code scanners are also available nowadays. Once a product is properly packed, it still needs to be stored and handled in a way as to prevent damage and potential cross contact with allergens. As a supplier, communication between company and buyers is crucial when there is an ingredient switching and formula update.

Food allergen management in the restaurant

Restaurants are becoming increasingly common for subsequent allergic reactions though the first exposure to allergic foods is often happens at home [116], the reactions can be very severe [117] due to the poor food allergen management in the restaurant. There are various reasons for restaurants operator failing to provide a safe meal for allergic consumers, such as a high rate of turnover of staff and gaps in restaurant staff's knowledge of food allergy; poor communications about food allergy between consumers and food handlers in the restaurants; cross-contact of foods (e.g. sharing utensils and containers); and hidden ingredients [120,115]. There are currently limited countries that have policies and/or educational programs to regulate the food allergen problem in the restaurant. Due to the mobility and low-tech nature of the restaurant's operation, employees' knowledge base of food allergy is limited [121-123]. There is only a brief requirement in the U.S that restaurant managers be able to "describe foods identified as major allergens and the symptoms that a major food allergen could cause in a sensitive individual who has an allergic reaction." in Food Code (2005)(<http://www.fda.gov/Food/GuidanceRegulation/RetailFoodProtection/FoodCode/ucm2016793.htm>), there are still no mandatory laws for retail food operations, except some guidelines. In the meantime, sensitive consumers need to be aware of the potential pitfalls in the restaurant and effectively communicate with food-handlers in order to safely enjoy the meals in the restaurants. It's ideal that restaurant could identify and remove unnecessary or unexpected allergens from their foods and avoid cross-containment. Some deemed management entails typically like:

- **Training.** Provide a relevant, cheap, and accessible while comprehensive, interactive training program to increase the basic awareness of food allergy for restaurant staff.

Displaying food allergy fact sheet is a good substitute to food allergy training program as to remind food –service personnel at any level when serving. The fact sheet should be able to (1) convey the severity of food allergies; (2) provide step-by-step food handling instruction on how to prevent cross contact and (3) provide solutions on how to handle the situation when consumer having food allergic reactions [120]. Established training programs, like the National Restaurant Association's ServSafe Allergens online course (<https://www.servsafe.com/allergens/the-course>), describe a range of distinct steps necessary to reduce the risk of food allergy adverse events in the restaurant. The restaurant's employees need to know their responsibilities regarding who and how to answer questions regarding menu items.

- **Prevent cross-contact.** There are a number of precautionary steps for food service workers to employ to mitigate risks when a customer with food allergies enters a restaurant. Complete a detailed Risk Assessment List (Table 2-2) for all products on site and prevent any identified cross-contamination hazard by implementation of appropriate control measures. Tips to avoid cross-contact in the restaurant setting can be found in Table 2-3. Dedicated attitudes when preparing meals and properly cleaning are essential to prevent cross-contamination. Cleaning the tabletops and utensils with validated methods is also an essential step in food allergen management in the restaurant. Studies have shown that conventional cleaning methods are effective in removing the protein of a food allergen such as peanut [124].

Before the meal preparation	Chef and food allergen expert have a meeting to review the menu, remove unnecessary food allergen in the recipe
During the meal preparation	Thoroughly wash hands with soap and water before touching allergen safe food Use separated or color coded utensils Allergen-safe food first Put allergen safe food away from allergen or cover it
After the meal preparation	Thoroughly clean the counter and utensils

Table 2-3 Tips to avoid cross-contact

- Effective communication.** In a highly complex and dynamic restaurant environment, cross contamination can happen everywhere, even if employees have already using uncontaminated ingredients and delivering an allergen-free meal using properly sanitized service ware, providing informative and easy-understanding food labels and having a conversation with the customer to clarify potential food allergy risk may still be helpful to protect allergic customers [125]. At the same time, as an allergic customer, it is also important to be aware of cross-contact when dining out. Individual should not feel embarrassed to ask and make sure they know the cross-contamination situation in that restaurant and what's inside their dish when dining out. It's better to ask in advance since sometimes it need more time when the information circles around from experts to service provider. As the food allergen management in the restaurant is far from perfect, patients themselves should take initiatives to remind the service provider of their disease and requirements. Simply wearing an alarm bracelet could be a useful way to alert the service providers.

Food allergen management in the school

Nowadays, the school lunch is commonly implemented in schools, which has the potential to increase the risk of accidental exposure to food allergens to sensitive students, there is an emerging need to address the issue of managing food allergy students in schools. It is reported that allergic children sometimes be bullied by their peers [126-128]. However, in the meantime, there is a great regional discrepancy of developing preventative measures to help sensitive students in the school, according to the study done by Kim et al's [129], there is only 17% of schools in Seoul, Korea that have some precautionary measures (e.g. notification for the inclusion of food allergens in school lunches) to reduce the risk. In the U.S, there are many voluntary guidelines for managing food allergies in school both in a national and statewide level. School food allergy management is mainly focus on reducing the risk of accidentally exposure to the allergens as well as properly treating allergic reactions and anaphylaxis when they happen. Communications among all levels of people plays an important role in food allergen management in the school. The parents must notify and cooperate with the school about their child's potential life-threatening food allergy. In the U.S, parents can fill out multiple forms of treatment plan with the help of school nurse such as the "individual emergency action plan" or "food allergy action plan" [50] in order to let the school be aware of their child's illness. Schools may establish a core team responsible for food allergy management and corresponding actions. A school nurse in collaboration with different personnel including the family of allergic students, physician, and teachers in order to develop an individualized food allergy treatment plan, the treatment will be reviewed periodically, especially after a reaction has occurred. One topic which is rarely mention in different guidelines is how to create an allergy friendly environment while allergic student

won't feel isolated, teenagers is a highly risk population due to their vulnerable state of mind, school staff should understand there is no "one-size fits all" approach to manage food allergies in school settings, and they need to react to students with food allergy with respect, some measures could be more tactfully executed include:

- **Education at all level.** Different groups of people should be aware of the individual with life-threatening food allergy and understand proper ways to prevent and handle the situation when severe reactions happen, these people should include (1) sensitive students and their peers (2) people who would contact to sensitive students including school bus driver, school staff, coaches, and after-school advisors.
- **Prompt access to epinephrine.** Immediate administer of epinephrine after the onset of severe food allergy reactions can save children's life. To ensure access to epinephrine within several minutes, a school should consider keeping a prescription for unassigned epinephrine for general use in a secure place and also allowing the student to carry auto injection device.
- **Enforce "no-sharing" policy.** Nowadays, with the increased awareness of food allergy, instead of orally educate children not to share foods with allergic peers, many elementary schools have designated a "peanut free" or "milk free" table in the cafeteria, some schools allow allergic students to eat in other rooms outside the cafeteria [130]. However, how to enforce these policies in a positive way without leading more conflicts between students should be carefully considered. No school should turn away a child solely because of the child's food allergies. It should be mentioned that children with life-threatening food allergies are considered disabled under the U.S federal civil rights laws, it's required that schools must provide accommodation to ensure the children participated fully and equally in all normal facets of the school day [130].

Maternity management

Some prevention practices for food allergy during or after pregnancy are still under debate for their efficiency. These practices include exclusive breastfeeding; maternal avoidance of allergenic food through pregnancy and during lactation, delayed introduction of solid food to the infants, mite avoidance, etc. [131-139]. However, there is still no decisive conclusion to support any practice as a standard precautionary way to prevent food allergy for children. For example, in 1998, the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT) (<https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cotstatements2008/cot200807peanut>), once recommended that avoiding eating peanuts and peanut products during pregnancy and lactation will prevent peanut food allergy for their children if pregnant women are atopic or the father or any sibling of the unborn child has an atopic disease. However, in 2008, after reviewing all the studies related to this topic, the committee admitted that this practice is no longer appropriate.

In another perspective, when dealing with the infants with diagnosed food allergies, one needs to be cautious to find alternative foods. For example, among infants with IgE-mediated cow's milk allergy, not all of them (10%) will tolerate a soy formula [140], at the same time, these infants can also react to partially hydrolyzed formula, lactose-free cow milk-based formula, and other mammalian milks (e.g. sheep, goat milks).

Chapter 3 Food Allergen Labeling around the World

Currently, since strict avoidance is still the only effective measure to prevent the occurrence of food allergies, appropriate labeling is considered the critical risk management tool in the food industry [141]. Originally, consumers with medical, religious, ethical and other dietary needs have been pressing for more detailed product information from the labeling [142], with more people caring about the food allergy issues, food allergen labeling is increasingly subject to legislative and regulatory scrutiny nationally and internationally, different groups have their own concerns about making food labeling regulations, so the regulations vary wildly across countries. However, with the globalization, international trade become increasingly frequent, the discrepancies in food regulations may set some barriers in trading food products among countries. Efforts are being made by many international, scientific and research organizations try to harmonize food regulations among countries.

When discussing current food allergen labeling issues, it's important to find out the current allergen labeling situation around the world. The following part provides an overview of existing international, regional and national regulations in 164 countries which are currently (Aug 2017) World Trade Organization (WTO) members. As of 2007, WTO member represented 96.4% of global trade and 96.7% of global GDP [143], the global regulatory environment of food allergen labeling regulations can be well-represented through the comparison of the regulations among these countries.

Methodology: the search process

Regulations on food allergen labeling were identified and verified through an extensive search of a range of sources to get the most accurate and up-to-date information, the primary source included:

- the agency and government websites
- legal texts and databases (e.g. FAOLEX; Global Legal Information Network);
- academic journals (using databases ScienceDirect, PubMed);
- literature citations and references in other documents
- magazine and newspaper articles (e.g. Selerant Compliance Cloud, Scribd)
- Internet search (www.google.com), Search keywords used were:

“allergen” or “allergy” or “hypersensitivity” and “food” and “label” or “labeling” or and each country’s name.

Codex Alimentarius guidelines were identified from the Codex Alimentarius website (www.codexalimentarius.net) as an international standard for food allergen labeling.

Nationally, the regulation information (laws, directives, guidelines, rules, and ministerial statements) on food allergen labeling of 164 current WTO members was collected, only 5 areas (Hongkong, Macau, Taiwan, Cape Verde and Liechtenstein) are current WTO members but not Codex members, which indicates that other 159 countries and areas generally agree with the ideas presented in the Codex Alimentarius. The search revealed the regulation systems in 151 countries and areas (13 countries and areas didn’t have any valid information). Regulations are listed in the following text as well as tables, the text is organized by WHO’s way of dividing the world into 6 regions (see Appendix 1) to better present the information.

The Codex Alimentarius

At an international level, Codex Alimentarius Commission (CAC) of the Joint FAO/WHO Food Standards Programme has developed a set of international standards, guidelines and related texts for food products. Codex is designated as the standard to solve international trade disputes by the WTO although the implementation of Codex Alimentarius is voluntary. Moreover, Codex also has profound guiding significance for countries to establish their own food safety system.

Among different standards, *General Standard for the Labelling of Prepackaged Foods* [80] developed by Codex Committee is relevant to food allergen labeling, in this standard, food allergen labeling information is contained in the “List of Ingredients” section, it clearly states that foods and ingredients that are known to cause hypersensitivity should always be declared. The CAC’s provisions for allergens include [144]:

- Cereals containing gluten; i.e., wheat, rye, barley, oats, spelled or their hybridized strains and products of these;
- Crustacean and products of these;
- Eggs and egg products;
- Fish and fish products;
- Peanuts, soybeans, and products of these;
- Milk and milk products (lactose included);
- Tree nuts and nut products; and
- Sulfite in concentrations of 10 mg/kg or more

The guideline provides flexibility for countries to make revisions according to their own needs.

Overview of national regulations

Summary

Overall, countries and areas can be characterized as having (1) mandatory food allergen labeling (2) voluntary food allergen labeling (3) no regulations. As shown in Table 3-1, 83 out of the 164 countries and areas reviewed in this paper have regulations on food allergen labeling. In countries with well-developed food allergen labeling requirements, they identify different priority allergens based on some concerns (mostly scientific research about allergen prevalence conducted in their countries). Other countries use an “adoption process” by fully or partially adopting one or several well-recognized regulations (e.g. regulations established by the European Union (EU) or Codex Alimentarius or U.S. Food and Drug Administration (FDA)) to follow. More detailed summary of the regulations is provided below, grouped by WHO regions. To be noted, only the regulations state that food allergens “must be” labeled will be considered as “mandatory food allergen labeling”, other words such as “should”, “shall” and “have to be ” will be considered as “voluntary food allergen labeling” if no other information is provided. For example, for Taiwan’s regulation, although it uses the word “shall” when describing labelling requirements, it has been considered as “mandatory food allergen labeling” in this article since it also mentioned in their regulation that “manufacturers that fail to provide complete or truthful information in product labels in accordance with these regulations shall be fined NT\$30,000-3,000,000 or NT\$40,000-4,000,000 respectively”.

Region(total/have regulations)	Mandatory		Voluntary		No regulation/No data found
African Region(41/2)	South Africa		Nigeria		32/7
Region of America(33/21)	Argentina Bolivia ^c Brazil Canada Chile ^c	Colombia ^c Costa Rica United States Venezuela	Barbados ^c Cuba Ecuador Jamaica El Salvador ^c Nicaragua ^c	Honduras ^c Saint Vincent and the Grenadines ^c Mexico Guatemala ^c Peru ^c Panama ^a	9/3
South- East Asia Region(8/3)	Thailand		Indonesia Myanmar		5/0
European Region(46/44)	EU ^g Iceland ^a Liechtenstein ^{a,b} Republic of Macedonia ^a	Norway ^a Switzerland ^a Turkey ^a United Kingdom ^a	Commonwealth of Independent States ^d Georgia ^e Montenegro ^a Ukraine ^a		2/0
Eastern Mediterranean Region (14/10)			Morocco Pakistan Gulf Standardization Organization ^f Tunisia		4/0
Western Pacific Region(22/14)	Australia Japan Malaysia Taiwan ^b	Singapore ^c South Korea New Zealand Vietnam ^c	China Hong Kong, China Laos	Mongolia Papua New Guinea ^c	6/3

^a Countries follow EU standard

^b Country/Area is not the member of WHO, put in corresponding region according to their geographical location

^c Countries follow Codex

^d Full list of 7 Commonwealth of Independent States member states can be seen in Appendix 2

^e While Georgia is not belong to Commonwealth of Independent States, it uses their food allergen labeling standard

^f The GCC Standardization Organization (GSO) is a standards organization for the member states of the Gulf Cooperation Council (Bahrain, Kuwait, Oman, Qatar, Saudi Arabia, United Arab Emirates) and Yemen

^g Full list of 27 EU member states can be seen in Appendix 2

Table 3-1 Summary of international food allergen labeling regulation status

African Region

- East African Community countries (Kenya- Uganda-Tanzania- Burundi-Rwanda) currently have no direct regulation for food allergen labeling, but they are in the process of harmonizing with the Codex [145].

- In Nigeria [146], it requires voluntary declaration of ingredients that are known to cause hypersensitivity, but the allergen list was not provided.

- In South Africa, food allergen labeling was developed over time; it has been modified to embrace more sources as food allergens which must be identified on the label with their new *South African food labeling and advertising regulations (R146)* passed in March 2010 [147].

- Countries like Zimbabwe and Senegal, it is said that their regulations adhere to the Codex Alimentarius, but in the corresponding food labeling regulations, they don't have particular content to describe requirements for food allergen labeling the same way as Codex [148].

Americas Region

- The United States is one of the countries with the most stringent food regulations, its food labeling system is also in a leading position around the world. In January 2006, U.S implemented the "*Food Allergen Labeling and Consumer Protection Act (FALCPA)*", the FALCPA requires that the labels of all pre-packaged foods regulated under the Federal Food, Drug, and Cosmetic Act (FFD&C Act) , if they contain one of eight “major food allergen” , the label must disclose the presence of the allergen in "plain English”, no matter how small the amount is, for example, if spices and pigments contain any one kind of allergens, it must

be indicated on the label. Among the “Big 8”, some of them are food groups, in this case, a specific spice of foods needs to be declared (e.g. indicate “Salmon” rather than “Fish” on the label) [149]. Although sulfites is not one of the “Big 8”, U.S asks to declare sulfites when the concentration in the food is above 10 ppm in Code of Federal Regulation Title 21, but the regulation doesn’t mention the way how sulfites will be labelled.

- In Canada, researchers conducted a survey in order to explore the epidemiological data of food allergens in 2008. Canada’s Amendments to the *Food Allergen Labelling Regulations in Canada Gazette, Part II (CGII)* came into force in August 2012, food allergens listed in the regulation are required to carry a label [150]. Three other foods were added to Codex in order to meet the needs of the Canadian population.

- Latin American has 22 countries, with 20 countries currently being WTO members, to the best of my knowledge, Suriname does not have any data online. Regulations on food allergen labeling among the remaining 19 countries and areas range from none (Belize) to mandatory labeling (e.g. Brazil).

- Among the five countries (Argentina, Brazil, Paraguay, Uruguay and Venezuela) which are current MERCOSUR (Common Market of the South) members, Argentina [207] and Brazil [151] moved to a mandatory food allergen labeling system in the past two years. In Venezuela, their regulation *Venezuelan Standard for the General Labeling of Prepackaged Foods (COVENIN 2952:2001-1st Revision)* [152] states food allergen must be labeled. In this regulation, the use of precautionary statements is explicitly permitted. While in Paraguay and Uruguay, they do not have their local laws to regulate the declaration of food allergens. In this region, MERCOSUR is proposed to harmonize the labeling of food allergens, but the discussion is slow due to the conflicts in their member countries.

■ 7 countries including Nicaragua, Honduras, Guatemala, Panama, Costa Rica, Belize, El Salvador are recognized as Central America, Guatemala, El Salvador, Nicaragua, Honduras, and Costa Rica have formed Council of Ministers of Economy (COMIECO) and has a technical regulation [157] dealing with labeling of prepackaged food. Since this regulation is an adaptation of Codex, it has the same major food allergen list and is recognized as voluntary food allergen labeling. In Costa Rica [210], in their own food laws, the major food allergen list is a subset of Codex's list. Panama's [213] allergen list is the same as EU.

■ Other Latin American countries, Colombia [153] and Chile [154] both ask for mandatory food allergen labeling. In Mexico [155], Bolivia [156], Peru [212], they generally follow Codex requirements. The enforcement strength (whether it's mandatory or voluntary) is decided upon the wording of the regulation. Ecuador states that their labeling requirements are based on Codex and FDA stipulations although it doesn't specifically mention food allergen labeling in the text.

- Caribbean countries now have 11 countries in the WTO, most of them were identified with no data or has no regulations on food allergen labeling (e.g. Antigua and Barbuda, Dominica, Dominican Republic), Saint Vincent [158] and Barbados [159] follow Codex; In Cuba [217], their food law doesn't specifically mention food allergen labeling, but it states that if discrepancies exist with other foreign labels, they will refer to Codex and the regulation also states that they accept U.S food labeling standards; While in Jamaica [160], they ask that "presence of food allergen, gluten and sulphites" need to be declared, but no food allergen list is found in that regulation.

East Asia region

See in Western Pacific Region

Europe region

- Compared to Codex, EU food labeling standards are intended to better protect the interest of consumers, therefore, they have a long list of major food allergens. In 2000, the *Labelling Directive (Directive 2000/13/EC)* became the first legislation in the EU referring to allergenic foods. The *Labelling Directive* requires manufacturers to declare all ingredients presenting in pre-packaged foods sold in the EU with very a few exceptions [161]. Nowadays, the *EU Food Information for Consumers Regulation (No. 1169/2011)* (EU FIC) and *Food Information Regulation (FIR) 2014* also mentioned food allergen labeling issues. There are currently 14 allergens listed in Annex II (as amended by Commission Delegated Regulation No. 78/2014) and are recognized across Europe as the most common allergen and the declaration is mandatory on labels. According to No. 1169/2011 [162], since December 2014, instead of using an allergy box or statement, manufacturers and retailers are required to specially mark allergen in the ingredients list on all pre-packed foods in order to warn consumers the allergen information. As a former EU member, United Kingdom keeps using the EU allergen labeling requirements.

- Within the Commonwealth of Independent States (including 9 member states such as Russia, Kyrgyzstan etc.), they use a set of technical standards called *GOST* (Russian: ГОСТ). In *GOST R 51074:2003* [163], the common food allergens are listed, but food allergen labeling is not mandatory.

- As European Economic Area (EEA) states and candidates for accession of to the EU, Macedonia, Iceland, Norway and Liechtenstein stick to the EU legislation on foodstuffs,

in 2014, Macedonia introduced new food labeling rules [164], it is regulated that declarations should clearly indicate allergens with bold letters or marked in a different color. Montenegro is not an EEA states but it's a candidate for EU membership, they are in the movement of in line with EU regulations concerning labeling

(http://www.fao.org/fileadmin/user_upload/Europe/documents/Publications/AI_briefs/Montenegro_ai_en.pdf).

- On November 25, 2013, the Swiss Department of the Interior and the Federal Office of Public Health revised the federal ordinance concerning the labeling of food allergens: *Ordonnance du DFI sur l'étiquetage et la publicité des denrées alimentaires (817.022.21)* [165]. Even though Switzerland is not a member of the European Union, these revisions were consistent with the requirements of Article 21 under the EU Labeling Directive, which means that food labels must clearly indicate 14 common allergens by using a special font, character style (e.g., capitalized letters), background color or other appropriate means.

- In 2002, Turkey revised *Communiqué on Rules for general Labeling and Nutritional Labelling of Foodstuffs-2002/58*, in which it states the general labeling requirements that allergenic foods need to have mandatory labels. This rule complies with *Directives 2000/13 EC* and *80/232/EEC*. In 2006, the *Amendment- Communiqué 2006/34* establish a list of allergenic ingredient (Annex-8) [166], these major allergens must be clearly indicated on the label even if they are in an altered form.

- Ukraine doesn't currently have any clear regulations related to food allergen labeling, but according to *The Draft of Technical Regulation*, it said that it will meet the requirements of the European Parliament and the European Council [167].

Eastern Mediterranean Region

- Morocco enforced their food allergen labeling in 2013, a list of allergens was provided along with the approved decree. The list is similar to EU standard but mollusks were not recognized as a priority allergen in the new decree [168].
- Gulf Standardization Organization has published *GSO 9/2013 on Labelling of Pre-packaged Foodstuffs for Gulf Cooperation Council (GCC)*, in this regulation, the priority food allergen list is similar to EU standards, but walnuts and clams are specifically mentioned as priority food allergens in this region. The labeling is voluntary [169]. As a member country, Saudi Arabia has its own priority list, which is a subset of the list provided in GSO 9/2013 [169].
- In Tunisia [170], while ingredient list is mandatory on the labeling, the regulation states ingredients that cause allergenic reactions should be conspicuously labeled. With no further information about what's the priority allergen list, it is considered voluntary allergen labeling in this paper.

Western Pacific Region

- Australia and New Zealand have uniform labeling requirements developed by Food Standards Australia New Zealand Food Authority (FSANZ). In Australia and New Zealand, any ingredients listed as food allergens in the *Food Standards Code* must be declared on the label no matter how small the amounts are. In 2016, some foods and ingredients derived from allergenic sources (e.g. fully refined soy oil, distilled alcohol from wheat or whey) did not require mandatory labeling after safety assessment. In the regulation, royal jelly is required to have a warning statement [171]. The Allergen Bureau has the

guidance for voluntary statements of allergen caused by cross-contamination which is not regulated by the *Food Standards Code*.

- China's Ministry of Health published its *General Rules for the Labeling of Prepackaged Foods* which needed to be adopted by April 20, 2012. In this standard, the common food allergens listed are adopted from the Codex, however, food allergen labeling is voluntary.

- Japan always attaches great importance to their food safety and security issues, their research on food allergen started relatively early; in fact, Japan was the first country that required mandatory allergen labeling. In 2000, the revised *Food Sanitation Act* clearly stated that the labeling on the container and packaging must indicate the potential sources of allergens. Japanese allergen labeling embraced two groups of labeling: mandatory labeling and recommended labeling. The most updated regulation till now (Nov 2016) contains 27 kinds of foods, among them, seven kinds of foods are required mandatory labeling, and the other twenty foods are recommended to carry an allergen labeling. The recommended labeling list keeps being updated, “cashew nut” and “sesame” were the newest foods that are added to the recommended allergy labeling list in August 2014.

- In South Korea, food items known to be food allergens must be indicated on the label even if they are added at minimal levels as part of a mix. On April 8, 2015, Ministry of Food and Drug Safety announced the expansion of food allergen labeling scope and revised the labeling methods for allergens. This revised regulation will be formally implemented as of the date of the announcement for foods manufactured or imported for the first time after the announcement. This new regulation will be applicable to all other foods from 2017 onwards. Previously, the labeling of 13 categories of allergens was required, including eggs,

milk, buckwheat, peanuts, soybeans, wheat, mackerel, crab, shrimp, pork, peaches, tomatoes and sulfite. The new regulation adds walnuts, chicken, beef, squid, oyster, abalone and mussel as mandatory labeled items when used as food raw materials. Moreover, rather than indicating in the ingredient statement, there should be a separate area on packages specifically designated for allergen labeling and the color of allergen warnings should contrast with overall package color [172].

- In Taiwan, the Food and Drug Administration of Taiwan's Ministry of Health and Welfare have promulgated the *Regulations Governing Food Allergen Labelling* which took effect on 1 July 2015 [173]. In the regulation, it stated that substances “shall be” prominently labeled if they may cause an allergic reaction, it was regard as mandatory labeling since non-compliance with the regulation will lead to fines. To be noted, mango, as a fruit, is considered as a major allergen for Taiwanese which is rare to see in other countries’ regulations.

- South Asian, as one of the most populous regions in the world, has great global trading potential [174]. Eight countries in this area including Afghanistan, Bangladesh, Bhutan, India, Nepal, Maldives, Pakistan and Sri Lanka formed South Asian Association for Regional Cooperation (SAARC) in order to promote free-trading among member countries. In this region, food labeling requirements are not well-developed. Afghanistan has no food law yet. In Bangladesh, Bhutan, Nepal, Sri Lanka, they don’t have any requirements for allergen labeling within the relevant food laws. In India, presently there is still no mandatory labeling of food allergens in food products except for infant milk substitute. As per *Food Safety & Standards (Packaging & labelling) Regulations, 2011*, the mandatory labeling of allergenic foods has been specified for Infant Milk Substitute; Clause 7 of Regulation No.

2.4.1 states “The container of hypoallergenic milk formula meant for infants with milk allergy shall indicate conspicuously “HYPOALLERGENIC FORMULA” in capital letters and statement “TO BE TAKEN UNDER MEDICAL ADVICE” [175]. In this region, Pakistan is the only country has some guidance for food allergen labeling, their food laws are based on Codex.

- Southeast Asia

10 countries in Southeast Asia named Laos, Malaysia, Vietnam, Singapore, Cambodia, Thailand, Brunei, Myanmar (Burma), Philippines and Indonesia formed another cooperative organization called the Association of Southeast Asian Nations (ASEAN). In 2005, the food experts in ASEAN drafted and finalized the *Guiding Principles for Food Control Systems*, which included the regional requirements for the labeling of pre-packaged foods. They share the same common allergens with Codex since the generic labeling requirements are adopted from Codex [177].

While individually speaking, in Thailand, allergen information was required to be displayed on the food label [176], the common allergens were derived from Codex guideline. Although all species belong to one food group need to be labeled, within the crustacean products category, the regulation provided 4 examples (crab, shrimp, Mantis shrimp, lobster) which was different from CODEX (no example was provided), although there was no information about why these 4 species were specifically listed. It is hypothesized that it may be related to some epidemiology data in this country.

Brunei Darussalam, Laos, Cambodia have no food regulations related to food allergen labeling. In Malaysia [215] and Vietnam, it is compulsory that ingredients known to cause hypersensitivity be declared on the label; In Singapore [216], the major allergens are same as

Codex, however, different from Codex, the regulation gave detailed explanation to each food group; The major food allergen in Indonesia [206] is similar to Codex with small modification, it replaced Crustacean to shellfish and sulfites only need to be labeled when >100 pm which is 10 times of what's on the Codex. Although in Philippines's food regulation, it doesn't specially states allergen labeling requirements, manufactures in Philippines widely used U.S labeling standard.

- Mongolia and Papua New Guinea are considered as implanting voluntary food allergen labeling requirements and follow Codex according to Gendel's paper [141], the evidence that Mongolia follows Codex standards is that in one of the Mongolian technical regulations, Codex was cited by reference.

Discussion

With the public awareness of the potential mortality associated with the food allergy increasing, more governments and manufacturers have taken initiatives to notify consumers about possible hazard of allergens in their products through labeling. Despite the consistent efforts to improve food allergen labeling, food allergic individuals still report having accidental exposure to an allergen attributed to labeling-related issues (Table 3-2) [107, 178], there are hundreds of food recalls annually in North America due to undeclared allergens [179-181].

Allergen is listed on the labels but not noticed by consumers	Allergen is not written in plain language
	Allergen is not clearly visible (same font size as other ingredients)
Allergens is not declared on the label	e.g. natural flavoring contains tree nuts but does not indicate “tree nut” as part of “natural flavoring”
	Unintentional cross-contamination during manufacturing
Over declare of allergens on the label	e.g. Use highly refined peanut oil but list “peanut oil” as an ingredient on the label
	e.g. frequent ingredient supplier change while using the same labels to reduce label cost, labels indicating all allergens the product may contain

Table 3-2 Food label related issues

For individuals, the biggest barrier is how to correctly decipher food labels. In U.S, although the labeling are required to be written in plain English, consumers still have confusion about “usual or common” names of ingredients. For example, in one study, 22% of parents can correctly identify all 7 products that contained soy, while 7% of parents correctly identifying all 14 labels containing milk. The correction rate also related to how many labels

they ask to decipher [182]. Table 3-3 shows ingredient derived from milk, it's hard for general public to recognize these ingredients are from milk without certain food science background.

Contain milk: Artificial butter flavor, butter fat, buttermilk, casein, caseinates (sodium, calcium, etc), cheese, cream, cottage cheese, curds, custard, Half&Half, hydrolysates (casein, milk, whey), lactalbumin, lactose, milk (derivatives, protein, solids, malted, condensed, evaporated, dry, whole, low-fat, non-fat, skim), nougat, pudding, rennet casein, sour cream, sour cream solids, sour milk solids, whey (delactosed, demineralized, protein concentrate), yogurt

MAY contain milk: brown sugar flavoring, natural flavoring, chocolate, caramel flavoring, high protein flour, margarine, Simplese

Table 3-3 Examples of ingredient derived from milk
(<https://kellymom.com/store/handouts/free-handouts/>)

As discussed above, there is a wide disparity between different countries with regards to the regulations that govern food allergen labeling, many countries haven't developed any food allergen labeling regulations. Among countries with some forms of regulations, significance differences exist, variations are mainly focused on three aspects (1) What are "common allergens"; (2) Whether the food allergen labeling is voluntary or mandatory; (3) What's the scope of food allergen labeling. These variations may be attributed to many factors including but not limited to (1) the choice of different existing guidelines to refer to when preparing national or regional regulations; (2) the country (or area)'s varying legislation and administrative systems involved when creating the regulations (3) nation (or area)'s different historical, political, cultural and economic environment.

What are “common allergens”

There is a significant difference among countries as to what allergens are disclosed in the regulations. As discussed previously, specific food allergen prevalence in a country is influenced by many factors including cultural difference, dietary habits etc., as early as 1999, the joint FAO/WHO Codex Alimentary Commission agreed to recommend labeling of main 8 foods known to be allergens. From then on, some countries took measures to tackle food allergen labeling issues in their own countries. For countries with developed food allergen labeling regulations, they usually have done plenty of research in order to decide which substances are their priority allergens, however, what criteria were used to develop the priority allergens lists isn't often provided in the public-access materials. Different organizations and authorities are responsible for developing legislations for their country regarding to food allergen labeling. For example, in 2002, Japan became the first country in the world to have mandatory food allergen labeling, their labeling system is decided by a labeling study group consisting of experts and stakeholders from different fields including clinical experts, patients, food experts, retailers and food industries [183]. By the time the regulation was first introduced, they had 5 allergenic ingredients which were required to be mandatorily labeled and another 17 ingredients are recommended to be labeled. There are now 7 kinds of food that have mandatory labeling and another 20 kinds of food that are recommended to carry a label. In U.S, the fundamental food allergen labeling legislation- *Food Allergen Labeling and Consumer Protection Act (FALCPA)*, was passed due to the efforts of some non- profit organizations dedicated to food allergy advocacy such as Food Allergy & Anaphylaxis Network (FAAN) and Center for Science in the Public Interest (CSPI). Some countries may have their own allergy bureau and food allergy

educational website in order to better deal with food allergen issues and educate their citizens. However, for most countries in the world, food allergen labeling issues are not formally discussed or food allergen labeling regulations remain unchanged since first established.

Since Codex is designated as the international food standards, most of the countries adopted allergen labeling regulatory framework directly from Codex, some countries developed their own regulations based on Codex and made some modifications, a complete list of foods that are currently identified as priority allergens in the countries (areas) with mandatory allergen labeling is shown in Table 3-4. From the table, we can see foods like egg, milk, peanut, tree nuts, soybeans, crustacean, fish are identified as allergenic substances almost universal in countries with mandatory food allergen labeling regulations. In addition to these 7 foods, several other foods are recognized as being associated with causing severe allergic reactions and be identified as priority allergens in two or more countries such as buckwheat, molluscan shellfish, mustard, and sesame. For example, buckwheat is required to be labeled both in Japan and South Korea, while sesame seeds are required to be labeled in Australia/New Zealand, EU and Canada. Some countries and areas also identify substances unique to their own country, such as the mango in Taiwan, lupin and celery in EU; pork, peaches, tomatoes, chicken, beef, squid, oyster are exclusively listed as priority allergen in South Korea. Generally speaking, countries belonging to the same region often share similar priority allergens. Fruits as major allergens are often identified in Eastern countries but are rare in Western countries.

In order to make the regulations concise and representative, many food allergens have been listed as priority allergens in a food group (e.g. tree nuts, fish, and shellfish). Although the intention is unclear, different countries will choose different items to explain the meaning

of a food group (Table 3-5), for example, in Codex, there is no example when describing “Crustacean and products of these” as one of the major food allergens, while in Thailand, the example for “crustacean and products of these” including crab, shrimp, Mantis shrimp, lobster. In order to clear up the confusion, some countries will only choose a specific food rather than a food group as their major food allergen. Instead of “crustacean and products of these”, Japan identify shrimp and crab as two of their seven major food allergens. There is also divergence on the definition of the same allergen categories. Only 8 named species are considered to belong to the group of “tree nut” in EU standards, while Canada has 12. In the US, a complete list is provided in a supporting document while 3 species are given as examples in formal food allergen labeling regulation. Pine nuts are considered to be seeds in EU (not a tree nut) while they are classified as tree nuts in some countries like USA and Canada. In the USA, some other products also considered as “tree nuts” including coconut and lychee. This suggests that the use of term “tree nut” is not uniform among countries, it’s generally based on common sense rather than strict botanical or anatomical structures. Countries like US and Canada with developed food allergen labeling regulations have stated in their regulations that specific species need to be identified on the label, without thoughtful consideration, many regulatory frameworks do not mention how to present the food group on the label.

	Codex ^a	U.S.	Canada	Argentina	Brazil	New Zealand/ d/	EU	Japan ^e	Malaysia	South Korea	Taiwan	Thailand	Costa Rica	Venezuela	South Africa
Cereals containing	X	Wheat	Wheat	X ^c	X ^c	Wheat	X ^c	Wheat	X ^c			X	X	X ^c	Wheat
Eggs	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Milk	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Peanut	X	X	X	X	X	X	X	X	X	X	X	X	X		X
Fish	X	X	X ^b	X	X	X	X		X	X ^c		X	X	X	X
Crustaceans	X	X	X ^b	X	X		X ^c	X ^c		X ^c	X ^c	X		X	X
Shellfish/Mollusk/Soy	X	X	X ^b	X	X	X ^c	X		X	X ^c		X		X	X
Tree Nuts/Sesame	X	X	X	X	X ^c	X ^c	X		X	X ^c		X		X	X
Mustard			X				X								
Celery							X								
Lupine			X			X	X								
Sulfites	>10mg/kg		X	>10mg/kg	X		>10mg/kg			>10mg/kg		>10mg/kg			
Other				Tartrazine	Natural rubber			Buckwheat		X ^f	Mango				

^a The following countries have the same priority allergens as CODEX: Chile, Bolivia, Colombia, Vietnam, Singapore

^b Seafood(shellfish, fish, and crustaceans) is considered as priority allergen group by Health Canada

^c Specific spices provided in Table 3-5

^d Royal jelly is required to have a warning statement.

^e Labeling is recommended but not required for abalone, squid, salmon roe, oranges, kiwifruit, beef, walnuts, salmon, mackerel, soybeans, chicken, bananas, pork, matsutake mushrooms, peaches, yams, apples, gelatin

^f Other includes buckwheat, pork, peaches, tomatoes, beef, chicken

Table 3-4 Priority Allergens among Countries with Mandatory Allergen Labeling

Counties	Codex	U.S.	Canada	Argentina	Brail	EU	NZ/AS	Japan	Malaysia	Singapore	South Korea	Taiwan	Thailand	Venezuela
Cereals	Cereals containing gluten; i.e., wheat, rye, barley, oats, spelled or their hybridized strains	Wheat	Wheat	Same as Codex		Cereals containing gluten namely wheat (such as spelt and Khorasan wheat), rye, barley, oats and their hybridised strains	Wheat	Wheat	Cereals containing gluten including wheat, rye, barley and oat	Same as Codex	Wheat	/	Same as Codex	Processed food products containing grain gluten (wheat, rye, oats, barley, spelt or any grain hybrid or product)
Tree Nuts	NE	Including 19 kinds of nuts ^a	12 kinds of nuts provided ^b	almonds, hazelnuts, chestnuts, walnuts, pine nuts,	10 kinds of tree nuts provided	Almond, hazelnut, walnut, cashew, pecan nut, Brazil nut, pistachio nut and Macadamia nut (Queensland nut)	27 kinds of foods and ingredients provided	Cashew nut	NE	Same as EU	walnuts	/	e.g. almond, walnut, pecan	NE
Crustaceans	NE	FDA's Seafood List	19 kinds of Shellfish and Crustaceans provided ^c	NE	NE		Complete list provide	Crab, shrimp ^e	/	Crayfish, prawns, shrimps, lobsters, crabs and	crab, shrimp, squid	Crab, shrimp	e.g. crab, shrimp, Mantis shrimp, lobster)	NE
Shellfish/ Molluscs	/	/	19 kinds of Shellfish and Crustaceans provided ^c	/	/	/	Complete list provide	/	/	/	/	/	/	/
Fish	NE	FDA's Seafood List	Including 44 kinds of species ^d	NE	NE	NE	Complete list provide		NE	Molluscs such as oysters,	Mackere	/	NE	NE

^a Almonds, Beech nut, Brazil nut, butternut, cashew, chestnut (Chinese, American, European, Seguin), Chinquapin, Coconut, Filbert/hazelnut, Ginko nut, Hickory nut, Lichee nut, Macadamia nut/Bush nut, Pecan, Pili nut, Pistachio, Sheanut, Walnut (English, Persian, Black, Japanese, California), Heartnut, Butternut

^b Almonds, Brazil nuts, Cashews, Chestnuts, Hazelnuts (filberts), Hickory nuts, Macadamia nuts, Pecans, Pine nuts (pinon, pignolias), Pistachios, Shea nuts (shea butter),Walnuts

^c Abalone, Clam, Crab, Crayfish (crawfish, écrivisse), Cockle, Conch, Limpets, Lobster (langouste, langoustine, coral, tomalley), Mussels, Octopus, Oysters, Periwinkle, Prawns, Quahaugs, Scallops, Shrimp (crevette), Snails (escargot), Squid (calamari), Whelks

^d Anchovy, Bass, Bluefish, Bream, Carp, Catfish (channel cat, mud cat), Char, Chub, Cisco, Cod, Eel, Flounder, Grouper, Haddock, Hake, Halibut, Herring, Mackerel, Mahi-mahi, Marlin, Monkfish (angler fish, lotte), Orange roughy, Perch, Pickerel (dore, walleye), Pike, Plaice, Pollock Pompano, Porgy, Rockfish, Salmon, Sardine, Shark, Smelt, Snapper, Sole, Sturgeon, Swordfish, Tilapia (St. Peter's fish), Trout, Tuna (albacore, bonito), Turbot, White fish, Whiting

^e Abalone/ Squid / Salmon roe/Salmon are proceed as recommended allergen labeling

Table 3-5 Examples of food groups in countries with mandatory food allergen labeling

On many country's regulations, sulfites and gluten are considered as major food allergens and subject to food allergen labeling regulations, however, as mentioned in the "Food allergy definition" section, the mechanism of adverse reactions to sulfites is unclear, while reactions to gluten are not Ig-E mediated. Further discussion need to be taken to decide whether it's appropriate to include sulfites in the food allergen labeling regulation and if not, how to regulate label sulfites existing in the products. In the meanwhile, it also easily causes confusion when the priority allergen list includes cereal grains. Countries like the USA specifically recognize wheat as a major food allergen and have separate regulations for gluten labeling, but other countries (such as the EU, Codex, Australia/New Zealand) may regard all the grains containing gluten as a priority allergen group, which make it tricky to label cereals like "oats" as some of the oats are gluten-free. There is little epidemiology evidence to show that there is widespread allergy to grains expects those who are sensitive to gluten [184], and needless to emphasis, gluten- intolerance is food intolerance rather than IgE mediated food allergy. In order to better protect consumers with Celiac disease, without listing the specific name of each grain, an alternate approach can be appropriate use of "gluten-free" mark on the label.

Unexpected potential complications may also exist on what's seems a "straightforward" item, such as "egg" and "milk". Countries like the U.S, the legal documents define "milk" as being cows' milk (21CFR131.110) and "egg(s)" as hens' eggs (21CFR160.115), while it can be that "milk" and "eggs" refer to products from all species in other countries [185]. Not long ago, Singapore updated their regulation [216], it clearly indicated that "egg and egg products" referred to "Eggs from laying hen, duck, turkey, quail, goose, gull, guinea fowl and their products", while "milk" including "Milk from cows,

buffaloes, goats and their products”. It can be foreseen that other countries will gradually update their food allergen labeling regulation since the current regulations are often times too abstract and nontransparent.

Nevertheless, in the great proportion of countries in the world, their priority now is not food allergy issues, without investing too much efforts and money, little is known about their major food allergens and if other native foods from this region are an important source of sensitization. Among these countries, some of them adopted requirements from Codex in order to obtain consistency with most trading partners and give a warning to most possible allergenic consumers. However, in a region with high cultural diversity, dietary habits and food preparation difference, food allergen epidemiology research still highly recommended for protecting patients with specific dietary needs.

Case study: Situation in China

As an increasingly strong economic body, there is a wide international trade between China and other countries. Comprehensive survey about prevalence data among all age group across China is unavailable, however, increasingly studies about allergen prevalence in different areas and different age groups are being done by different researchers. In Leung’s [186] study, prevalence rates of doctor-diagnosed food allergy rate among pre-school children is around 5%, and commonest foods are shellfish (15.8%), egg (9.1%), peanut (8.1%), beef (6.4%), cow’s milk (5.7%), and tree nuts (5.0%). One study investigated the prevalence of food allergies in Grades 1-5 students in the Beijing Shunyi district, showed that mango, shrimp, peach, milk, dairy products, mutton, fish, crab, and eggs were the main allergic food [187]. While in another study surveying students from China Medical University, the prevalence rates among young college student are 1.91%, major allergenic

foods are sea foods, milk [188]. The prevalence rate in children and adults is comparable to the rate in other countries, but the priority allergens are different, seafood and cow's milk are most prevalent in all age group in China based on the existing research.

Moreover, Chinese clinical reports indicated fruits as allergens which can lead to severe allergic reactions. Pineapple is specifically listed in China but not in other countries [189]. Some regionally favored food can also be threatened to sensitive people such as silkworm pupa, it's a custom unique for some Chinese people consuming silkworm pupa as food, silkworm pupa can be consumed either by oil-fried, water-boiled or ground pupa powder. Although treated with high temperature, the silkworm pupa can still be allergenic. It is important that people be warned fried silkworm pupa have been known to cause severe allergic reactions since it is estimated that each year in China, there are over 1000 patients who suffer anaphylactic reactions after consuming silkworm pupa. In one summary of 13 prior cases of severe anaphylactic reactions were caused by silkworm pupa consumption, the report time of onset and treatment of this illness is consistent with the general principles of having allergic shock. Following proper and timely therapy, patients who suffer an allergic reaction to silkworm do not exhibit sequelae [190]. Another cultural food allergy is bird's nest soup, which is made almost entirely from swifts' saliva (mainly glycoproteins extinction) [191].

Whether the food allergen labeling voluntary or mandatory

Unlike nutritional labeling, while the highest proportion of countries and areas requiring labeling on a voluntary basis [192], most countries with food allergen labeling regulations asked for mandatory labeling. However, the reasons for countries to favor mandatory allergen labeling are not well-discussed among different countries. Generally speaking, the major part of decision-making for national or regional standards involves a cost-benefit analyses process [193], it is questionable whether countries undergo such process when ask for mandatory food allergen labeling. While mandatory allergen labeling is an effective method to protect sensitive patients, mandatory labeling has the potential to reduce customers' incentives for purchasing and sets barriers for international trading. Moreover, the regulation of allergen caused by cross-contamination is not well-developed around the world. Likewise, the standards, verification process, labeling methods in requiring mandatory food allergen labeling are all under great debate and need more future research. Policy decisions should fundamentally be based on science, but what research results give the best guidance for food allergen labeling also need to be further discussed. In this respect, prevalence information, consumers' research, drawbacks of existing food allergen labeling policy should be taken into account. Since some existing regulations [183] about food allergen are based on analytical methods, it must be remembered that there is still a huge gap between existing allergen detection techniques and clinical reference effectiveness [194]. With the increased interest in food allergy, more information related to different food allergens come out frequently. However, cautions is needed when establishing a regulation since once the regulation has been passed and widely implemented, it lacks the flexibility to adapt new changes quickly.

Types of foodstuffs covered by food allergen labeling regulations

Different legislative organizations apply their regulations to different types of foods. In most countries, the requirements are limited to prepacked foods. However, the definition of prepacked foods may vary in different countries, and sometimes, discrepancy even exists within the same country. For example, in Canada, “prepackaged product” refer to products packaged for sale to consumers as well as those sale to other institutions or companies in *Food and Drug Regulations* (FDR)(FDR governed the allergen labeling in Canada), while in *Consumer Packing and Labeling Act* (CPLA), “prepackaged product” solely refer to the products sale to consumers. As discussed earlier, cross-contamination of food allergens are particularly serious in the locations such as restaurants and schools while the foods are provided without package. Some countries are considering expanding the scope of existing food allergen labeling regulation, for example, in EU, from December 2014, if the 14 allergens are used as ingredients, allergen information needed to be provided for foods sold without packaging or wrapped on site. This information could be written down on a chalkboard or chart, or provided orally by a member of staff, etc.

Exemption and addition

Exemption

Many countries state that allergenic ingredients must be declared no matter how small amount they are, however, the allergenic proteins could be removed, modified or degraded during processing and may no longer trigger allergic reactions in human bodies.

Acknowledging to this fact, the Codex labeling standard delegates consideration of future additions or exemptions to the allergenic food list. However, it does not indicate who is responsible for initiating such reviews or what process to use. Many countries specifically state in their regulations that some ingredients are automatically exempt from labeling requirements, such as highly refined oils. Some countries allow additional exemption from the compulsory labeling if they can provide sufficient safety assessment results. For example, in the U.S, exemptions can be achieved through either a petition or notification process when sufficient “scientific evidence” that ingredients will not “cause an allergic response that poses a risk to human health” are provided, a review team will be formed to evaluate the materials on a case-by-case basis, however, due to the deficiencies (data quality and incomprehensiveness) of the data provided, the exemptions are hard to achieve [195]. The EU allergen labeling regulatory framework has already included the exemptions when describing 14 major food allergens. However, it also has a similar process evaluation process to grant new exemptions. Till 2012, there have been 13 applications for ingredient derived from grains, fish, soy, milk approved [184].

Addition

Due to research advancement and eating patterns changing, there is a possibility to require labeling of additional allergenic foods. In the previous discussion, many countries have already added some allergenic ingredients to their regulatory framework after the implementation of the original food allergen labeling regulation. However, the organizations that are responsible for this issue and criteria that are used to enclose new food allergens are not articulated in most countries. Canada is the only jurisdiction that set detailed criteria for adding new foods to the priority allergens list. Their process of adding a potential priority allergen in the regulation including systematic reviews on the (1) “credible cause-effect relationship” (2) data on prevalence (3) potential exposure in the Canadian population (4) other concerns (e.g. potential hazard as “hidden ingredients”).

Ways indicating food allergens

Many regulations state that “food items are known to be food allergens must/shall be indicated on the label”, however, only a few regulations define the formal formats on how to present the information on the label. In real practice, manufacturers in different countries generally follow two ways: (1) conspicuously declare the presence of an allergen in the ingredient list, for example, the font can be bold, capitalized, and italic or using parentheses (2) use “contains” statement for allergenic ingredients. The word “contains” followed by the name of the food source from which the major food allergen is derived. This statement usually printed immediately or is adjacent to the ingredient list. In most countries, although not specifically mentioned, both of these two methods are permitted and no preference to use one method rather than another. For example, in the U.S, it states in the FALCPA that both of these two methods can be used. However, exclusive use of the first method has been required in EU from December 2014. Other than these two methods, some countries will use an allergen box which is considered as more visible to potential sensitive consumers.

Appendix 3 summarized different ways of declaring allergens on the label, which brings one concern that different people may have distinctive ways of interpreting the law. For example, it is believed that the allergen will stand out in the ingredient statement if the company uses method 1 to declare the allergen, however, actually the label is acceptable under the law once the allergen is listed in the ingredient statement, the company can list all ingredients using the same typography, for example, if milk is one of the ingredients of a product, once the “milk” is listed in the ingredient statement, it already fulfill mandatory food allergen labeling requirements, which make it extremely hard for susceptible people to recognize the presence of allergens when the products contain a lot of ingredients.

Hidden ingredients and Precautionary allergen labeling

Situation

As discussed in Chapter 2, allergens can accidentally be present in the product due to cross-contamination at many points during food production and distribution (Table 3-6). The hidden ingredients may not be explicitly listed on the label consciously or unconsciously [178]. Moreover, some allergens may still exist in the spices, flavorings, colors, or additives either due to (1) cross-contamination during processing or preparation or due to (2) the unwillingness of manufacture to completely reveal information about product composition [142]. Precautionary allergen labeling (PAL) was first introduced by the food industry as a useful strategy to help inform consumers the risk of reactions from the unintended presence of allergens in foods. Unlike the regulations on priority food allergens, the use of PAL is not regulated by legislation by the majority of countries around the world [116]. Although according to GMP, FDA advised that advisory labeling such as "may contain [allergen]" should not be used as a substitute for adherence to current Good Manufacturing Practices (cGMPs). In addition, any advisory statement such as "may contain [allergen]" must be truthful and not misleading, in real practice, the labeling for any addition of warning statement can only be achieved through the FSA Allergy Advisory Labelling Decision Tree assessment (see Appendix 4). Other authorities like the UK Food Standards Agency [172] and Health Canada [196] have also provided guidance regarding the use of terminology of advisory labels. However, studies have shown a high prevalence of using PAL on the label [119,120]. The problem is exacerbated by limitations associated with the current analytical methods for detecting allergens in food products and the diversity of PAL terminology.

Potential “hidden” Source of Food Allergens

Cross-contact (allergen source easy to be overlooked: air, packaging)
Ingredient switching/formula update (information lost within cross-functional team cooperation)
Cross-reactivity
Allergenic foods not covered by the labeling regulations in certain country
Undeclared allergenic source (e.g. international trade when two countries have different food allergen labeling laws)
Food aids, preservatives, additives, natural flavorings

Table 3-6 Potential “hidden” source of food allergens

There are many different varieties of statements (Table 3-7), the most common types are: (1) “may contain [allergen]”, (2) “manufactured on shared equipment with [allergen]”, (3) “manufactured in the same facility with [allergen]”, of those that had precautionary statements, “may contain traces of [allergen]” was the most common. Since PAL is mostly voluntarily and unregulated, it has been both over- and under-applied by the food industry at the same time, manufacturers tend to include PAL in their package in order to avoid posing risk on allergic costumers. It should be noted that it doesn’t show a satisfactory relationship between the presence of PAL and the actual risk of an unintended allergen. Some products without PAL may still contain sufficient allergen to trigger a reaction [197, 198]. In the consumer's perspective, they must make their own decisions on how to interpret these PAL statements, here are two common attitudes towards PAL, some cautious consumers may be overwhelmed since “trace allergen” labeling greatly decrease the number of food choice especially when PAL are on their everyday staples [107]. On the other hand, some consumers erroneously believe the wording PAL statements employed reflects a hierarchy of risk about

Examples of advisory warning on labels

May contain...

May contain traces of ...

Packed in an environment where... may be present

Made in a facility that also processes...

Produced in a factory which handles...

Produced on shared equipment which also process..

Made on the same production line as...

Made in production are that also use

No nuts ingredients, but cannot guarantee to be nut-free

Not suitable for.. allergen suffers

Due to methods used in the manufactures of this product, it may occasionally contain ...

May be present (use By VITAL™ 2.0)

Table 3-7 Examples of Advisory Warning on Food Labels

a degree of contamination [199], for example, many consumers believe that “may contain” indicating a higher risk than “may contain traces” [200, 201]. This tendency has recently been confirmed in a multinational survey conducted by the Patient Organization Committee of the European Academy of Allergy and Clinical Immunology. A similar result was showed on a survey asking consumers’ willingness to purchase products with different PAL statements , 16% of respondents reported that they would purchase food with a “may contain” statement, 25% would purchase food labeled “may contain traces” and 41% would purchase products labeled “manufactured in a facility that also processes allergen” [53]. Moreover, after safely consuming a product with PAL, some consumer may wrongly perceive they can tolerate traces amount of that allergen, which can lead to risky behavior in the future. Nowadays, with a proliferation of PAL, a significant proportion of food allergic consumers ignore PAL [202]. Some consumers may consider the change has been made purely to protect the food manufacturer from liability responsibilities [203].

Legal status

In current stage, public health authorities needs to work with industry to ensure the wording and presentation of PAL are in a clear and consistent manner, this would help healthcare professionals to be able to train their patients on how to utilize PAL as part of their own risk management strategy [204], great confusion exists now regarding to PAL for the healthcare professional and the consumer alike [7].

A number of studies have been performed trying to develop a standardized approach to improving the utility of PAL [117,118], however, there is still no consistent relationship between actual risk of cross-contamination and the terminology of PAL, as early as 2000, Switzerland became the first country to utilize a threshold to guide the use of PAL [204]. No labeling is required at levels below 10 mg/100 g (100 ppm) gluten for cereals or 1 g/kg (1000 ppm) for other allergens, however, there are no data assessing the effectiveness of such general threshold on the incidence of allergic reactions. In 2006, the UK Food Standards Agency produced a guideline in order to determine the risk of allergen cross-contamination and encourage the use of uniform wording of PAL [205], unfortunately, since the recommendation is voluntary, the actual enforcement was not ideal [110]. Some countries tend to strictly prohibit the use of PAL. In Japan, it's a legal process that the foods need to go through a quantitative test, the threshold is 10 microgram protein/g food weight (10 ppm), above which the labeling is mandatory if the food is one of the 7 priority food allergens [104]. In 2010, Argentina also prohibited the use of PAL in their legislation, but they don't provide the detection threshold for the exception [207].

Voluntary Incidental Trace Allergen Labelling (VITAL) is a new risk management tool developed in Australia recently for use by the Australian food industry to assist with

declaring the possible presence of allergens in their products. The VITAL process was developed with the intent of replacing all other forms of precautionary labeling, using a validated risk assessment tool to determine the need for precautionary labeling. The new system requires that cross contamination is equal to or above the action level, then ‘Maybe present’ statement is used as a precautionary statement to replace all statements, otherwise, no precautionary labeling is required [208]. Recently, VITAL was revised (VITAL 2.0) due to the increasing threshold data available, the initial VITAL had a 10-fold uncertainty factor applied in order to keep a conservative action level due to the limited minimum provoking doses existing at that time [209]. However, due to the voluntary nature of VITAL, it has some limitations to prevent the wide implementation of this process, in the industry perspective, they don’t gain any profits by following this process, in a consumer’s view of point, when the product have been subject to this assessment and revealed they don’t to carry the ‘May be present’ statements, they look identifiable to other products simply not carrying any PAL, consumers can’t make a safer choice by reading the labels of these two kinds of products.

Conclusion

Tremendous growth of knowledge and interest in the area of food allergy has been shown in the past few decades, more detailed information about epidemiologic data in different countries and immunopathologic mechanism at the molecular level has been intensively researched, scientists now have a better understanding of food allergy which leads to the development of improved methods for prevention, diagnosis, treatment and management.

The primary therapy for food allergy is still strict avoidance casual foods. There is no formal guidance on management practices in different settings. An educational program to increase food allergy awareness for employees and well-established food allergen control plan is recommended to prevent the occurrence of allergic reactions in these settings. People from different groups need to work together towards creating validated policies on food allergen management in different settings.

Clear and honest food allergen labeling is the only effective tool for risk management available to the sensitive consumer at this time. With globalization and increasing trade among different countries, a globally agreed food allergen labeling and precautionary food allergen labeling framework would enable foods produced around the world to be safely ingested by consumers around the world irrespective of allergy status in different countries. However, in order to achieve this goal, effective risk assessment methods should be created, validated and universally implemented. Cost-effective allergen detection assays and threshold levels for different causative foods and different populations are still under research.

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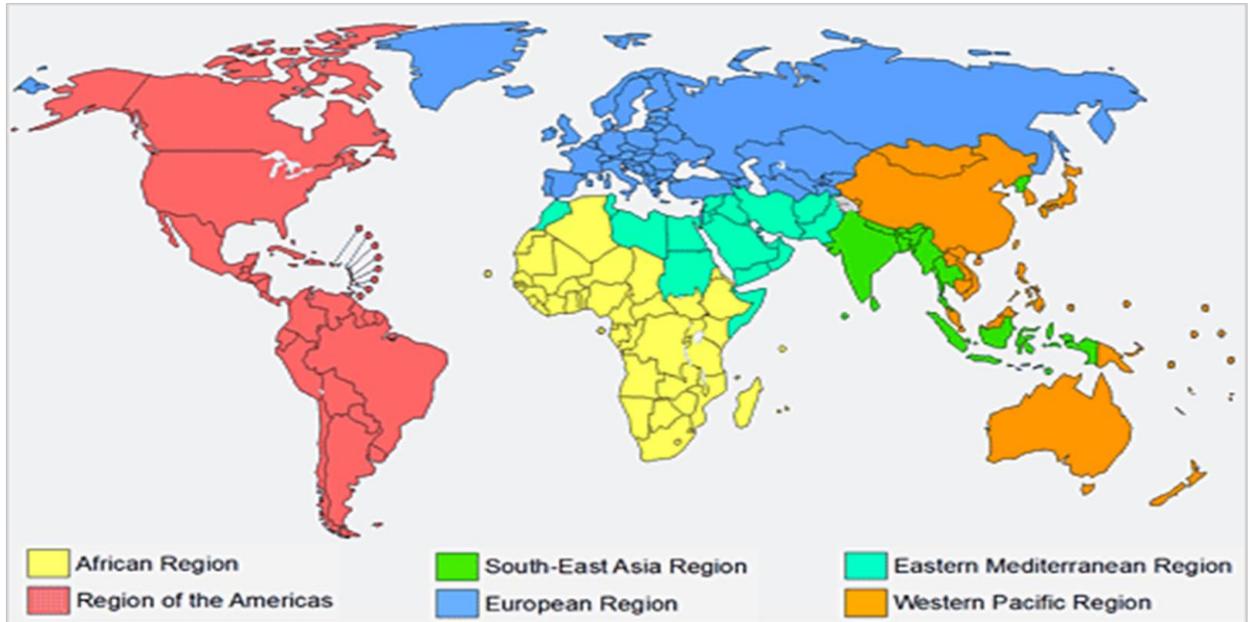
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Appendices

Appendix 1. WHO Reginal Map



Picture from: <http://www.who.int/about/regions/en/>

Appendix 2. Member States

EU member states (till Aug 2017)

Austria, Belgium, Bulgaria, Croatia, Republic of Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden.

Commonwealth of Independent States member states (till Aug 2017)

Armenia, Belarus (not WTO members), Kazakhstan, Kyrgyzstan, Moldova, Russia, Tajikistan, Turkmenistan (not WTO members), Ukraine, and Uzbekistan (not WTO members)

Appendix 3. Different methods of showing allergens on the labels

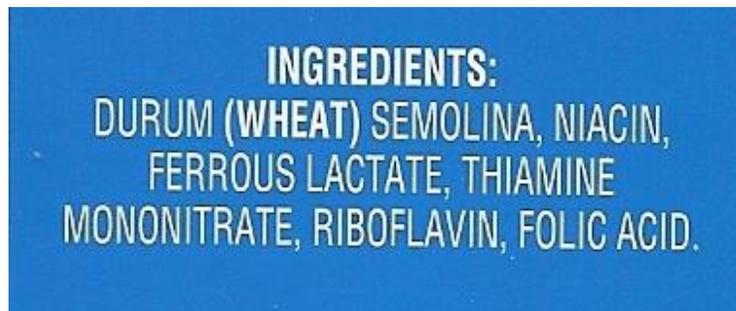
Using name that is recognizable to consumers

- **Ingridennts using common name, but not spefic listed**

INGREDIENTS: APPLE BRIOCHE ROLL (ENRICHED WHEAT FLOUR (FLOUR, NIACIN, REDUCED IRON, THIAMINE MONONITRATE, RIBOFLAVIN, FOLIC ACID), WATER, SUNFLOWER OIL, EGGS, DRIED APPLES, BUTTER (MILK), CANE SUGAR, APPLE BUTTER (APPLES, APPLE CIDER, CINNAMON), SALT, YEAST, CULTURED WHEAT STARCH, MALTED BARLEY FLOUR, AMYLASE), WHITE MEAT CHICKEN STRIPS RAISED WITHOUT ANTIBIOTICS (WHITE MEAT CHICKEN, WATER, SEASONING (DEHYDRATED GARLIC, DEHYDRATED ONION, SPICES, SUGAR, PAPRIKA), SALT, VINEGAR, POTATO STARCH, SEASONING (CHICKEN BROTH POWDER, CHICKEN POWDER, ONION POWDER, NATURAL FLAVOR), DEXTROSE, SUNFLOWER OR SOYBEAN OIL, SODIUM PHOSPHATE, SPICE EXTRACTIVES), SMOKED BACON (CURED WITH: WATER, SALT, SUGAR, SODIUM PHOSPHATE, NATURAL FLAVORS, SODIUM DIACETATE, SODIUM ERYTHORBATE, SODIUM NITRITE), NEUFCHATEL CHEESE (PASTEURIZED MILK AND CREAM, SKIM MILK, CHEESE CULTURE, SALT, STABILIZERS (CAROB BEAN AND/OR XANTHAN AND/OR GUAR GUMS)), MAPLE MUSTARD (DISTILLED VINEGAR, STONEGROUND MUSTARD SEED, SUGAR, SALT, MAPLE SUGAR, MAPLE SYRUP, SPICES).

(picture from Starbucks paninis ingredient Statement)

- **Common name to be listed in parenthesis after the less common name.**



(picture from : <http://www.allergyfreetable.com/FALCPA.php>)

- **Allergens are specific listed in the Ingredient Statement**

INGREDIENTS
Water, Carrots, Onions, Red Lentils (4.5%) Potatoes, Cauliflower, Leeks, Peas, Cornflower, Wheat flour, Cream (milk), Yeast Extract, Concentrated Tomato Paste, Garlic, Sugar, Celery Seed, Sunflower Oil, Herb and Spice, White Pepper, Parsley
ALLERGY ADVICE
For allergens, see ingredients in bold

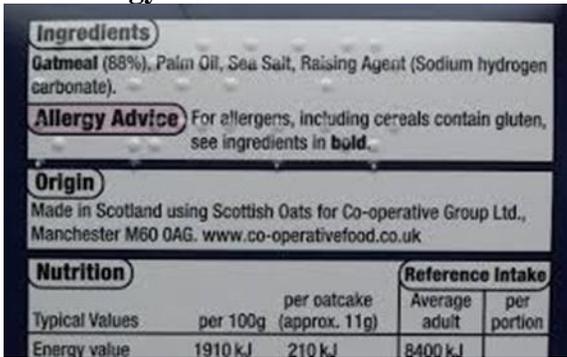
(picture from <https://maidahillchefs.wordpress.com/2015/09/06/food-allergies-and-food-intolerance/>)

Using “contains” Statement

SODIUM ALUMINUM SULFATE, CORN STARCH, MONOCALCIUM PHOSPHATE AND/OR SODIUM ACID PYROPHOSPHATE, CALCIUM SULFATE, DISTILLED MONOGLYCERIDES, ENZYMES, WHEAT STARCH, CALCIUM CARBONATE, ANTIOXIDANTS (TOCOPHEROLS, ASCORBIC ACID), CELLULOSE GUM, DOUGH CONDITIONERS [FUMARIC ACID, SODIUM METABISULFITE], PRESERVATIVES [CALCIUM PROPIONATE, SORBIC ACID AND/OR CITRIC ACID], COLE SLAW (COLESLAW MIX [SHREDDED GREEN CABBAGE, RED CABBAGE, CARROTS], COLE SLAW DRESSING [SOYBEAN OIL, SUGAR, WATER, CIDER VINEGAR, VINEGAR, EGG YOLK, SALT, CONTAINS LESS THAN 2% OF MUSTARD FLOUR, POLYSORBATE 60, XANTHAN GUM, NATURAL FLAVOR, CALCIUM DISODIUM EDTA (TO PROTECT FLAVOR)], MODIFIED FOOD STARCH). CONTAINS: WHEAT, EGG.

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Other methods

- Allergy Advice Box**


(Picture from: <https://dairyfreeswitzerland.wordpress.com/2014/11/23/new-requirements-for-food-allergen-labeling/>)
- Allergen diagram**


(Picture from: <http://justhungry.com/handbook/dining-out-japan/food-packaging-labeling-allergy-causing-food-substances-japan>)

Appendix 4. Allergy Advisory Labelling Decision Tree assessment [211]

