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Common Allergenic Foods and Their Labelling in Canada - A Review

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CONTENTS

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ABSTRACT

Objective: **To develop a scientifically based list of foods known to cause severe adverse reactions in hypersensitive individuals, which should always be declared on the labels of prepackaged foods.**

Options: **Consideration was given to those foods most commonly identified as causing medical problems that are seriously debilitating, life threatening, or are associated with increased risk of serious chronic disease.**

Outcomes: **Provision of more complete ingredient information on prepackaged foods for individuals with food sensitivities; reduction of food-related illness and possible fatalities; and a reduction in costs resulting from food recalls by food manufacturers and importers.**

Evidence: **A search of MEDLINE was conducted to identify studies on the foods most commonly involved in severe adverse reactions. Emphasis was placed on randomized, placebo-controlled clinical trials and case control studies, when available. International proceedings were reviewed. Articles were grouped according to the foods in question and the impact of labelling the proposed foods was examined.**

Values: **The working group (the authors) consisted of representatives of the Canadian Food Inspection Agency (CFIA), the Health Protection Branch, Health Canada, and a practicing pediatric allergist, in consultation with the Canadian Society of Allergy and Clinical Immunology, the Allergy/Asthma Information Association, the Canadian Celiac Association, and other experts in food allergies and sensitivities in Canada and the United States, and Canada's food industry.**

Benefits, Harms, and Costs: **Implementation of the recommendations would enable individuals with food sensitivities to choose a wider variety of safe, prepackaged foods; there would be potential for lower health care costs, fewer allergy investigations, fewer costly food recalls, less time lost from work, and fewer liability suits against food manufacturers. Costs to industry would involve stricter manufacturing procedures and analytical controls, and more complete ingredient lists on the labels of prepackaged foods.**

Recommendations: **1. The following foods and their derivatives, when added as *ingredients or components of ingredients* to prepackaged foods, should always be declared on food labels by their specific common names: *peanuts, tree nuts* (almonds, Brazil nuts, cashews, hazelnuts [filberts], macadamia nuts, pecans, pine nuts, pistachios, walnuts), *sesame seeds, milk, eggs, fish, Crustacea* (e.g., crab, crayfish, lobster, shrimp), and *shellfish* (e.g., clams, mussels, oysters, scallops), *soy, wheat, sulphites.* 2. The plant species should be identified in the common names on food labels of all forms of hydrolyzed plant proteins and starches and lecithin (e.g., hydrolyzed soy protein, modified wheat starch, soy lecithin). 3. Food manufacturers,importers, distributors, and food service establishments should develop an Allergen Prevention Plan to manage allergy risks.**

Validation: **These recommendations have been reviewed and fully endorsed by the Canadian Food Inspection Agency (CFIA), Health Canada, the Canadian Society of Allergy and Clinical Immunology, the Allergy/Asthma Information Association, and the Canadian Celiac Association.**

Sponsors: **The Canadian Food Inspection Agency (CFIA) and Health Canada.**

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INTRODUCTION

The Canadian *Food and Drug Regulations* (Canada, Health and Welfare) require most prepackaged foods to have a complete list of ingredients. These regulations, however, exempt certain foods and food mixtures from an ingredient list, and others from a declaration of their components (ingredients of ingredients). Also certain common names, which are allowed to be used on food labels, do not require

a declaration of the plant source, e.g., hydrolyzed plant protein. As a result of these regulations, certain prepackaged foods may contain undeclared ingredients or components that could cause severe adverse reactions in hypersensitive individuals. Cross-contamination before, during, and after manufacture is another major reason for antigenic ingredients being present, but undeclared, in prepackaged foods.

In 1993 Health Canada initiated a major review of the *Food and Drug Regulations*. During consultations with health agencies, consumers, industry, and government, numerous requests were made for more complete labelling of the foods most commonly involved in severe adverse reactions.

The Purpose of this Document is Therefore:

- to identify, from the scientific literature, the most common foods causing severe adverse reactions in hypersensitive individuals;
- to clarify the impact of present *Food and Drug Regulations* on the labelling of the proposed list of foods;
- to recommend changes to the *Food and Drug Regulations* to improve labelling of food ingredients known to cause adverse reactions in Canadians.

Scope of this Document

Consideration is given only to those foods most commonly identified as causing medical problems that are seriously debilitating, life threatening, or are associated with increased risk of serious chronic disease.

Consensus

The recommendations of the working group were reviewed and fully endorsed by the Canadian Society of Allergy and Clinical Immunology. Full endorsement was also given by the Allergy/Asthma Information Association and the Canadian Celiac Association. The recommendations were also endorsed by involved government departments.

History of "Allergen" Lists in Canada

Since its incorporation in 1970, the Allergy/Asthma Information Association has identified and provided information to Canadians about a variety of foods causing adverse reactions. In response to increased demands for information about possible "allergens" in restaurant foods, the Canadian Restaurant and Foodservices Association, in cooperation with the Department of Health and Welfare Canada, the Allergy/Asthma Information Association, and the Canadian Society of Allergy and Clinical Immunology, developed a list of foods commonly involved in adverse reactions.[1] In 1991, the Allergy Aware Program,[2] was launched in a number of Canadian restaurants, in which various "allergens" were identified in menu items (Table I).

In preparation for the introduction of an Allergy Beware Program in 1993, the then Grocery Product Manufacturers of Canada, in conjunction with the Allergy/Asthma Information Association and the Department of Health and Welfare Canada, developed a list of the most common foods causing anaphylaxis in Canada (Table I). This voluntary program was developed to make food production companies more aware of the impact of food allergens, and to develop strategies at the plant level to reduce the possibility of undeclared allergens being present in foods.[3]

In 1993, the Codex Committee on Food Labelling, of the international Codex Alimentarius Commission, discussed a proposal to amend the Codex General Standard for the Labelling of Prepackaged Foods, which included a proposed list of allergenic foods that should always be identified on food labels.[4] This list was subsequently revised and a draft list of the foods most commonly involved in severe adverse reactions was accepted in principle by the Codex Committee on Food Labelling in 1998.[5] The development of specific criteria for making additions/deletions to the Codex list of food allergens is in progress. Table I compares this proposed Codex list with others from Canada, the United Kingdom, and the United States.

Terminology

The terminology surrounding adverse reactions to food has been very confusing.[6] The following terms, as used in this paper, are adapted from Anderson.[7]

Adverse Food Reaction (sensitivity): a general term that can be applied to a clinically abnormal response to an exposure to a food or food component. This term includes both food allergy and food intolerance.

Food Intolerance: a general term describing an abnormal physiologic response to an ingested food or food component. This reaction is not proved to be immunologic, and can include idiosyncratic, metabolic, or toxic responses to food or food components.

Food Allergy (hypersensitivity): an immunologic (usually IgE-related) reaction resulting from the ingestion and in some cases skin contact or inhalation of a food or food additive, and is unrelated to any physiologic effect of the food or food component. This term may include any food reaction known to involve an immune mechanism, e.g., celiac disease.

Food Anaphylaxis: severe, sometimes fatal, allergic reaction to food, in which the immunologic activity of IgE antibodies and the release of chemical mediators are involved.

Table I Comparison of the most common foods and food ingredients causing adverse reactions

Food Group	FAO/WHO Codex Committee on Food Labelling (proposed)[5]	Canada				UK	USA
		Allergy Aware[2]	Allergy Beware[280]	Canadian Paediatric Society[56]	Health Canada and CFIA (proposed) (1999)	Hide et al., 1994[281]	USFDA[282]
cereals	cereals containing gluten i.e., wheat, rye, barley, oats, spelt, or their hybridized strains and products of these	corn, wheat, gluten			wheat	wheat	wheat
fish	Crustacea and products of these; fish and fish products	fish, seafood	fish, shellfish	fish, shellfish	fish, Crustacea, and shellfish		fish, Crustacea, mollusks
eggs	eggs and egg products	eggs	eggs	eggs	eggs	eggs	eggs
legumes, seeds	peanuts, soy beans and products of these; tree nuts and nut products	peanuts, soybeans, nuts and seeds	peanuts, nuts	peanuts, tree nuts soy	peanuts, tree nuts, sesame seeds, soy	peanuts, tree nuts, soy	peanuts tree nuts soy
milk	milk and milk products (lactose included)	dairy products, lactose		milk	milk	milk	milk
sulfites	sulfites >10 mg/kg	sulphites	sulphites		sulphites		
others		animal fats and oils, MSG, tartrazine					

Clinical Manifestations of Allergic Reactions

Allergic reactions to foods usually involve the glycoprotein portion of a food,[8] and may be described as classical Type I IgE-mediated reactions. Such reactions can range in severity from a skin rash or slight itching of the mouth, to migraine headaches,[9] to anaphylactic shock and death.[10] The route of allergen administration, dosage, frequency of exposure, and genetic factors all determine the type and severity of an individual's allergic response.[11] Although a wide variety of foods have been reported to cause allergic reactions,[12] this paper deals with those foods most commonly reported.

Anaphylactic reactions to foods are unexpected and frequently occur within minutes of ingestion, but occasionally the initial reaction may delay as long as 4 hours. Reactions may be biphasic, with delayed symptoms appearing many hours after the initial reaction.[13] Except in a few cases, the reaction does not last more than 24 hours.[14,15] First observed symptoms may be on the lips, tongue, palate, and throat, and are often characterized by itching, hives, and/or swelling. Entry of the food into the stomach and intestine may cause cramping, nausea, pain, and diarrhea.[16] Subsequent systemic symptoms can involve almost every organ of the body, although the pulmonary and cardiovascular systems are the ones most commonly affected.[10,17] The most dangerous symptoms include breathing difficulties and a drop in blood pressure or shock.[18]

Exercise-induced anaphylaxis, sometimes triggered by the ingestion of wheat, shellfish, celery, and other foods, has been reported.[17,19-22] Exercise-induced anaphylaxis is discussed further under cereals.

Other adverse reactions to foods, although not IgE-mediated, can also be very severe. They may be chronic in nature and can seriously affect the quality of life. For example, consumption of wheat, rye, oats, barley, and triticale increases the risk of lymphoma and osteoporosis in individuals with celiac disease.[23,24] Intolerance to milk, which is a common form of adverse reaction in children, can result in failure to thrive, unless adequate substitutes are given.[25] Most reactions to sulphite are not IgE-mediated, but can be fatal.[26]

Incidence of Adverse Reactions to Foods

Little precise information is available on the incidence of severe and fatal reactions to foods in Canada, the United States, or other countries, or on the costs associated with such reactions to foods.[27] However, a recent report from the United States indicated that food allergy is the cause of 33% of emergency visits for treatment of anaphylaxis, and peanuts and tree nuts are the foods most often associated with these severe reactions.[28] The severity of anaphylactic reactions varies greatly, and data on the prevalence of anaphylaxis and incidence of anaphylactic reactions are dependent on the inclusion criteria chosen.[29-30] As a result, widely differing incidence and prevalence data are reported.[31] In addition, until recently there has been no code for anaphylaxis in the International Classification of Diseases,[15,32] and because of this, fatalities from food-related anaphylaxis may sometimes be recorded as death from asthma or heart failure.[33] A standard protocol for assessing these patients and a nationwide study of the incidence of food anaphylaxis are needed.[12]

Early incidence figures reported from Finland estimated the prevalence of food allergy at 19% at age one, which increased to 27% at three years, and dropped to 8% at six years of age.[34] Much lower figures were reported in a prospective trial in the United States, which found that 8% of the children under three years of age had an adverse reaction to at least one food.[35] Other authors estimate 2% to 3% of the pediatric population and 1% to 2% of the adult population in the United States suffer from allergic reactions to foods.[8] A double-blind placebo-controlled food challenge (DBPCFC) study in the United Kingdom estimated that the prevalence of reactions to eight foods varied between 1.4% and 1.8%. The foods tested were cow milk, egg, wheat, soya, orange, prawns, nuts, and chocolate.[36] It has been suggested that these figures may seriously underestimate the prevalence of adverse reactions to foods in the UK.[37,38] A best-guess estimate of food allergy prevalence among children in the United Kingdom is less than 4% to 5%.[39] A report from the Netherlands estimated that food allergy and intolerance may affect 2.4% of the adult Dutch population.[40] A recent survey of 33,100 individuals in France estimated the prevalence of food allergies at between 2.1% and 3.8%.[41]

It is widely recognized that atopic illness is increasing.[42] This may be partly due to greater awareness and better diagnosis, but additional explanations might include early exposure of infants to a wider variety of allergens, with possible sensitization of the fetus during pregnancy[25,43,44] and of the baby during breast-feeding.[45,46] Modifications to the allergenicity of foods during processing is also suggested as a possible reason for an increase in food allergies.[47] The value of allergen avoidance during pregnancy and lactation and by atopic children has been of interest for many years.[48] A recent prospective controlled study involving food allergy avoidance examined the development of atopy in 165 high-risk children. The treated group consisted of mothers who avoided cow milk, egg, and peanut during the last trimester of pregnancy and during breast-feeding. The children avoided cow milk to age one, egg to age two, and peanut and fish to age three. The controls consisted of mothers and infants who followed standard feeding practices. Despite a significant reduction in food allergy and milk sensitization prior to age two in the treated group, by the age of seven no differences were noted between treated children and controls with respect to food and aeroallergen sensitization, food allergies, atopic dermatitis, and asthma.[49]

Anaphylactic reactions to foods also appear to be increasing,[15] with an estimated minimum of 950 anaphylactic reactions occurring annually in the USA.[32] In Ontario, Canada, there were seven fatal anaphylactic reactions to foods between 1986 and 1991 in children of school age,[50] and others have occurred since. Numerous factors have been reported to contribute to the increase in anaphylaxis including: previous food anaphylaxis, asthma, lack of awareness of the seriousness of food allergy by the person with the allergy or by others, denial of symptoms, failure to inquire about ingredients in foods, inadequate labelling of foods, and inadequate early treatment with epinephrine.[51] The early introduction of antigens into the fetus from the mother's diet or via breast milk are suggested as other possible factors.[25,44,52-54]

Avoiding foods known to cause anaphylaxis is best, but if anaphylaxis does occur, epinephrine (adrenaline) followed by hospital emergency assessment and monitoring is the treatment of choice. Fatal outcomes are most often associated with either not using epinephrine or a delay in its use.[55,56] Most allergists recommend that individuals with anaphylaxis carry self-administered epinephrine in preloaded syringes (e.g., Ana-Kit, EpiPen). It should be noted that not all ambulances in Canada are currently equipped with epinephrine.

It has been predicted that as more protein substances, such as milk- and egg-based fat substitutes,[15] and unlabelled proteins such as milk protein[57] are added to foods, the incidence of anaphylaxis will continue to rise. The need for accurate labelling of foods[57,58] and more data on the incidence and changing patterns of food allergies and intolerances has been stressed.[36,39]

Until the early 1980s, the relationship between food and adverse reactions was based primarily on clinical observations and circumstantial evidence. Skin prick tests have been found to be of some help in diagnosing IgE-mediated reactions to foods, but they tend to result in a high rate of clinically insignificant positive skin tests and a small but significant rate of false negatives.[59]

Radioallergosorbent testing (RAST), an in vitro assay for the detection of specific IgE antibodies, has a similar or slightly lower sensitivity than skin prick testing.[60] In 1983, the use of a DBPCFC categorically established the relationship between food and allergy. In this test neither the physician nor the patient knows which patient receives the antigen or the placebo. DBPCFC is now regarded as the "gold standard" by the American Academy of Allergy and Immunology for establishing the relationship between foods and adverse reactions to them.[25] However, DBPCFC is tedious, difficult to implement, should be carried out in a hospital or clinical research setting, and has been described as more of a bronze than a gold standard.[39]

It is interesting to note that individuals' perceptions of their allergies and those of their children often do not closely correspond with the allergies proven by DBPCFC.[61-63] Also of interest is a recent study which indicated that anaphylaxis is probably not linked to sudden infant death syndrome (SIDS).[64]

Strategies to prevent children with severe food allergies from being exposed to a variety of allergenic foods at school, especially peanuts, are being developed in Canada,[65-67] the United States,[18,68-71] and abroad.[72] The Canadian School Boards Association, representing almost 500 school boards in Canada, recently produced national guidelines to help protect school children from allergens such as peanut.[66]

Common Allergenic Foods

Food allergies are more common in children than in adults, probably because of a more immature gut which is more permeable to undigested proteins.[10] In infants and children, the majority of allergic reactions are to milk, peanuts, and eggs, and to a lesser extent soy and wheat.[45] Although most of these allergies, especially to egg, milk, soy, and wheat, usually disappear by three years of age, some individuals continue to have severe reactions to these foods into adulthood. The foods most commonly associated with allergic reactions in individuals over three years of age are peanuts, tree nuts, fish and shellfish, and eggs, and they are usually life long allergies.[73] It should be noted that severe allergic reactions to certain foods can also develop in adults who previously tolerated these foods well.[74]

Most of the DBPCFC data for food allergies in the United States have been for children. An analysis of the data in 1992 indicated that only seven foods accounted for nearly 95% of the reactions. In descending order of frequency they were: egg (25%), peanut (24%), milk (23%), tree nuts (10%), soy (6%), fish (3%), and wheat (2.5%).[25] In a 16-year study of 480 children with adverse reactions to foods, 11% had adverse reactions to more than one food.[45] In a report of seven fatal food reactions in older children and adults in the United States, the foods implicated were peanut, crustaceans, tree nuts, and fish.[75]

Although reactions to specific foods may vary to some extent from one country to another,[39] there are remarkable similarities among the most common foods reported to be causing severe adverse reactions in Canada, the USA, and the UK (Table I). Recent data from other countries indicate that: in Australia, most frequent food allergies among children are egg (3.2%), milk (2.0%), peanut (1.9%), and sesame (0.4%)[42]; in Britain, peanut allergy now affects approximately 1% of all preschoolers[44]; and in France, among children with food allergies, 40% had an allergy to egg, and 28% to peanut.[41]

The Canadian Pediatric Society has listed peanuts, tree nuts, soy, milk, eggs, fish, Crustacea, and shellfish as the foods most commonly involved in adverse reactions in children in Canada.[56] Following is a review of each of these foods, along with a discussion about other foods and food ingredients commonly reported to be involved in allergy and intolerance reactions.

Review of Foods Involved in Adverse Reactions

Peanuts

Peanuts belong to the legume family. Large quantities of peanuts are consumed both in Canada and the United States, with about half being in the form of peanut butter.[76] Peanut protein has been described as the most dangerous of all food allergens.[11] Yunginger et al.[75] reported on 7 fatal anaphylactic reactions, 4 of which resulted from peanut consumption. Sampson et al.[15] described 6 fatal and 7 near-fatal cases of food-induced anaphylaxis. Four of the 13 cases resulted from peanuts, and 3 of them were fatal. Reactions to the smell of peanut butter have been reported in sensitive individuals.[76] Peanut allergy is presenting earlier in life. It has been theorized that some babies may be sensitized to peanuts in utero,[25,77] and in some cases it is suspected that sensitization may occur from peanut protein in breast milk, as a result of peanut consumption by nursing mothers.[46] It appears that highly atopic infants are at special risk for sensitization to peanuts.[78] Peanut and tree nuts were incriminated in the deaths of 6 out of 7 children who died of anaphylaxis in Ontario, Canada between 1986 and 1991.[50]

In a recent study from France, the following clinical features of peanut allergy were reported: atopic dermatitis (40%), angioedema (37%), asthma (14%), anaphylactic shock (6%), and digestive symptoms, including abdominal pain and vomiting (1.4%).[79] In an unpublished prospective study of 1081 food-allergic patients, it was found that 21% of all patients diagnosed with peanut allergy developed anaphylactic reactions.[80]

Peanut proteins have been classified as albumins, which are water soluble, and globulins, which are soluble

in saline solutions. The globulins, which comprise about 87% of the total seed proteins, are composed of two fractions, arachin and conarachin. Two purified subfractions of these proteins, *Ara h* I and *Ara h* II, have been reported to be highly allergenic.[81,82] These two fractions have been identified, characterized and partially sequenced. *Ara h* I, a vicilin-like storage protein,[81] has a mean molecular weight of 63.5 kDa and an isoelectric point of 4.55. *Ara h* II, has a mean molecular weight of 17 kDa and an isoelectric point of 5.2.[82] Both *Ara h* I and *Ara h* II have been shown to have multiple IgE binding domains.[11,83]

In a recent study, 14 peanut-allergic subjects were tested with a randomized DBPCFC using doses of peanut protein ranging from 10 µg to 50 mg. The threshold dose varied among the study group, with as little as 100 µg of peanut protein provoking subjective symptoms in one peanut-sensitive individual.[44] This study reveals that extreme care is needed by food manufacturers and restaurateurs to minimize the risk of cross contamination of foods with peanut protein.

A variety of methods for detecting peanut protein in food samples have been developed and others are presently under development. In 1996, using a peanut-specific polyclonal antibody, Health Canada scientists developed a quantitative immunoassay for peanut protein with a detection limit of 0.4 ppm.[84] The method was subsequently licensed and a commercial test kit is being developed. Canadian Food Inspection Agency (CFIA) laboratories are presently using a semi-quantitative ELISAtest kit (ELISA-TEK) for testing suspected food samples. This test kit is similar to the Health Canada immunoassay, with an estimated detection limit of 0.5 ppm. Another test kit based on the work of Hefle, is a sandwich ELISA with a sensitivity ranging from 2.5 to 25 ppm.[85] Another new test is a rapid dipstick ELISA immunoassay, recommended for detecting peanut contamination in raw materials, processes and products, with a reported detection capability of 100 ppm peanut protein in marzipan, and 1000 ppm in chocolate.[86] A relatively low cost peanut method using rocket immunoelectrophoresis (RIA), capable of detecting 10 ppm in chocolate samples, has also been developed for use by food control agencies, and in routine quality control by industry.[87]

Peanut protein is very heat stable, but it does lose some of its allergenicity during roasting.[88] Peanut allergen has been reported to occur only in the seeds of this legume, and not in the stalks, leaves, roots, or flowers.[89] Refined peanut oil is generally thought to be free of allergenic protein,[77,90] however, the presence of peanut allergen in peanut oil has been reported.[31,41,91,92] It is not clear which processing techniques reduce the protein or alter the allergenic epitopes on peanut protein.[93] However, cold-pressed, expelled, extruded, or unprocessed peanut oils can contain significant amounts of peanut antigen,[94,95] as would oil in which peanuts were roasted.[88] Because of the possibility of the presence of peanut protein in cold-pressed peanut oils, and peanut oils in imported foods, Canada's *Food and Drug Regulations* now require that all forms of peanut oil, including modified, hydrogenated and partially hydrogenated, be identified by plant source on food labels.[96]

Of concern for peanut-allergic individuals are peanuts that have been pressed, deflavored, reflavored, and made to look like other nuts such as almonds, walnuts, pecans, etc. They have sometimes been identified as mandelona nuts, which is not an acceptable common name on food labels in Canada. It has been reported that such products retain their severe antigenicity.[88]

Some peanut-sensitive individuals may also be allergic to one or more tree nuts. One study has recently reported that 50% of those allergic to peanuts also reacted to almonds, 40% to cashews, 30% to pistachio nuts, 26% to Brazil nuts, and 21% to hazelnuts.[41] Cross-reactions with other legumes, including lentils, soy beans, green beans, kidney beans, navy beans, black-eye peas, green peas, and licorice (a member of the pea family),[25] and sweet lupine[97] have also been reported. However, this cross-reactivity is infrequent, with one study reporting only 2 out of 41 (5%) legume-reactive children being allergic to more than one legume.[98] Reactions to specific foods may also vary to some extent from one country to another.[39] For this reason, instructions to avoid all foods in a food group should always be based on tested immunologic response and oral challenge, and not just botanical relationships of the foods in question.[99]

Apparent resolution of peanut allergy has been noted in a small number of young children affected by peanut allergy at a young age.[53,100] However, developing such a tolerance to peanut protein is rare, and most peanut-allergic individuals must avoid all traces of peanuts for life. This may not be as easy as it sounds. In a study of 32 children (1 to 14 years) who were allergic to peanuts, 75% accidentally ingested peanuts during the five years preceding re-evaluation, despite the efforts of all the children and their families.[101]

Attempts have been made to desensitize individuals with severe peanut allergy using rush immunotherapy. This procedure involves a series of injections of peanut extract, but the procedure must be done where highly trained intensive care staff and emergency equipment are available, since allergic reactions to peanut immunotherapy may occur.[102] Although injections of peanut extract have been shown to increase tolerance in some peanut anaphylactic patients, induced tolerance could not be maintained in very sensitive individuals, using the peanut extracts that are presently available.[103]

A novel form of immunotherapy using anti-IgE antibodies to inhibit IgE synthesis and function is being studied for the treatment of IgE-mediated disorders.[104] Whether this therapy can be successfully used to reduce peanut anaphylaxis remains to be seen.

Tree Nuts

Tree nuts are estimated to be responsible for 10% of all severe adverse reactions to foods in the United States.[25] The main tree nuts of concern include almonds, Brazil nuts, cashews, hazelnuts (filberts), macadamia nuts, pecans, pine nuts (pignolias), pistachio nuts, and walnuts.

In a study of 14 children with 19 DBPCFC proven reactions to nuts, the varieties of nuts involved were: walnut (7), cashew (6), pecan (3), pistachio (2), and filbert (1). In the group, one patient reacted to five varieties of nuts, one patient to two varieties and the others to only one variety each.[101] Of the seven fatalities from anaphylaxis reported by Yunginger, one resulted from ingestion of pecans.[75] Of the six fatal and seven near-fatal anaphylactic reactions to food in children reported by Sampson, three fatalities resulted from peanut, and two from cashews. The near-fatal reactions included two from filbert, and one each from peanut, walnut, and Brazil nut. Five of the fatalities took place in public places, four at school, and one at a fair.[15] A death from hazelnut anaphylaxis resulting from 6 mg of hazelnut in a chocolate has been reported from Sweden.[105] A study from the UK has reported anaphylactic reactions to a variety of nuts. The worst reactions to nuts among 172 patients were caused by the following: Brazil nut (9), pistachio (4), walnut (3), almond (3), cashew (3), hazelnut (1). Among this group was one fatal reaction resulting from ingestion of walnut.[31]

Compared to peanuts, less research has been done on the allergens of tree nuts. A study of 12 people with Brazil nut allergy was reported.[106] Ten of these individuals were atopic and all of the patients had an allergic reaction within three minutes of exposure. None of the five patients, who were followed up for eight years, had lost sensitivity to Brazil nuts. Co-existing allergies with other nuts was noted in six patients: peanut (5), hazelnut (2), and walnut (1). Immunoblotting was used to isolate four important groups of proteins in Brazil nuts.

Pistachio nuts, which are a member of the *Anacardiaceae* family, are reported to contain several antigens with molecular weights ranging from >14.2 to 70 kDa. Other members of this plant family are poison ivy, cashew, and mango. Cross-reactivities among pistachio, cashew, and mango seed, but not mango pulp, have been reported.[107]

Pine nuts have also been reported to cause severe allergic reactions in a few individuals.[108-112] Increased allergenicity of pecans due to the formation of neo-allergens during heating and storage has been reported.[113] Certain amino acid sequences in walnuts are reported to be very similar to those of the vicilin group of seed storage proteins.[95] Like peanut allergy, the allergy to tree nuts is usually lifelong.[114]

Seeds

Severe reactions to sesame seeds[50,105,115,116] and sesame oil[117] have been reported. One death of an asthmatic child in Ontario was attributed to sesame seed anaphylaxis.[50] An early report[118] stressed the seriousness of sesame allergy, at a time when sesame oil was widely thought to be a safe vehicle for hormone and penicillin injections. Malish et al.[115] reported IgE antibodies to sesame seed in three of four patients with suspected anaphylactic reactions to sesame seed and unrefined sesame oil. These authors determined the molecular weights of IgE-binding antigens, and found several antigenic components in sesame seed extract, ranging in molecular weight from <8 to >125 kDa, with the most active allergens in the range of 8 to 62 kDa. Researchers have reported that two proteins, a 14 kDa and a 25 kDa, are most commonly involved in sesame allergenicity.[119] A high degree of cross-reactivity has been reported among sesame seeds, poppy seeds, kiwi fruit, hazelnut, and rye grain.[120]

Reported symptoms to sesame seeds and oil include stinging of the lips, hives, asthma,[121] plus contact dermatitis from sesame oil, as well as anaphylactic shock to both oil and seeds.[50,116,117]

The incidence of sesame allergy appears to be increasing, likely as a result of sesame seeds and oil being used in a wider variety of foods.[119] In France, nine cases of individuals with proven sesame allergy were tested with DBPCFC using oral doses of sesame seed flour. The most sensitive patient developed hives and pharyngeal itching with 100 mg of sesame seed flour and 3 mL of sesame seed oil.[122] Sesame seed has only recently been introduced as a common food in Australia, but is now the fourth most common cause of food allergy in Australian children, with a prevalence of 0.4%, compared to egg (3.2%), cow's milk (2.0%), and peanut (1.9%).[42] This figure represents a higher sensitization than to any one tree nut. It appeared that 60% of the children had been sensitized to sesame by two years of age, and one 11-month-old infant developed edema and hives when given his first taste of tahini, a food which his mother had reported eating during pregnancy and lactation.[123]

A patient with a serious sesame seed hypersensitivity, but with a negative skin test response and no demonstrable specific IgE antibodies in the serum, was reported.[124] One of 65 cases of food-related anaphylaxis in Sweden was due to sesame.[105] Nine systemic allergic reactions to sesame seeds were reported in Switzerland between 1978 and 1991.[116] Two cases of anaphylaxis to sesame were recently reported in England.[31] Criteria to be used for inclusion of foods in a priority list of allergens, using sesame seed as an example have been discussed.[125]

Severe systemic reactions to cottonseed protein have been reported in seven subjects who consumed a fiber bar containing cottonseed protein,[126] and one person consuming a whole grain bread containing cottonseed protein.[127]

Soy

Soybean allergy is considered to be the fourth most common childhood food allergy, after peanuts, cow's milk, and egg.[128] Soybeans, which belong to the legume family, have been used for infant feeding by the Chinese and Japanese for centuries. One report on severe reactions to foods that have been confirmed by DBPCFC in the United States indicated that 6% were caused by soy.[25] One fatal and one near-fatal anaphylactic reaction to soy in hamburger, and one fatal reaction to soy in meat kebabs have been reported in Sweden.[105] The children involved had severe asthma in combination with allergy to peanut. Soy cross-reactivity with peanuts, peas, and beans has been reported, but is not as frequent as was previously believed.[99] However, unlike peanut, an adverse reaction to soy is often lost spontaneously.[129]

An earlier report identified the Kunitz soybean trypsin inhibitor as a specific allergen in soybeans.[130] It now appears that soybean allergy involves several major allergens, and that soybean-allergic individuals might react to quite different soybean proteins.[128] An ELISA for measuring one of the major allergens in soy bean (*Gly m* Bd 30K) has been reported.[131] In preliminary results, the allergen was measured in a range of 5 to 500 ng. A commercial kit for detecting soy in food samples, with a detection limit of 0.5% to 1%, has been developed and is available from Cortecs Diagnostics, Deeside, UK. Another more sensitive immunoassay with a detection limit of 2 ppm has recently been developed for routine surveillance, by industry and regulatory agencies, of the presence of raw or cooked soy in a food matrix.[132]

There have been conflicting reports on the allergenicity of soy oil, with one report indicating detection of soy protein in soy lecithin, soy margarine, and occasionally soy oil,[133] and another reporting that soy oil is not allergenic to soy-sensitive individuals.[134] Soy lecithin has been reported to be an occupational allergen in bakers' asthma.[135] Of interest was a recent study that reported no detectable soy protein in the meat of chickens fed a diet containing 25% soy bean meal.[136]

Children who are allergic to cow milk are often given soy-based formulas. Like milk, large quantities of soy can result in a transient soy protein-induced gastroenteropathy with resultant chronic diarrhea and failure to thrive. Estimates of the number of children who have either IgE-mediated reactions or gastroenteropathy from both milk and soy, range from 10% to 30%.[137] Extensively hydrolyzed casein formulas are often recommended for these children.[138]

Soy bean products are widely used in formulated foods for their functional properties such as texturizing, emulsifying, etc., and are often not recognizable as soy.[139] For this reason it is very important that they always be identified on food labels.

Milk

Milk sensitivities are complex and are often not well understood. They are of three types: milk allergy, milk intolerance, and intolerance to lactose.[25,140] Unlike IgE-mediated milk reactions, milk intolerance reactions can begin several hours or days after ingestion of moderate and large amounts of milk.[42]

Adverse reactions to milk are reported to be the most common food sensitivity observed by pediatricians in the United States, with a reported prevalence in children as high as 7.5%.[25] A conservative estimate of cow milk allergy among children in the UK was reported to be 2% to 3%.[39] Milk hypersensitivity in adults, occurring as gastrointestinal reactions, may be more common than previously thought.[141]

Milk allergy. Various protein allergens are contained in milk, with casein and beta-lactoglobulin reported to be the most allergenic in oral challenge and skin tests, followed by alpha-lactalbumin.[142] It has been reported that the predominant allergen in adults with IgE-mediated allergy to cow milk is casein.[143] Heat treatment can reduce the antigenicity of whey proteins, but has almost no effect on the antigenicity of casein.[144] In a report on six milk-allergic children who had reacted to "non-dairy foods," an ELISA for the detection of casein with a detection limit of 10 ng/mL was used to confirm milk protein contaminants.[57] Since then more sensitive test kits with a detection limit of 0.08 ng/mL for polyclonal antibody assay[145] and 0.002 ng/mL for monoclonal antibody assay[146] have been developed. A report from Sweden has indicated that 10 mg of casein caused an allergic reaction requiring medication, and milk in a sausage, equivalent to 60 mg of casein, resulted in fatal anaphylaxis.[105]

IgE-mediated milk allergy develops more frequently in babies with atopic dermatitis and may be triggered by trace amounts of cow milk antigen, which may be passed to the baby through the mother's breast milk from dairy products she has consumed, or from feeding cow's milk to the baby.[147] A study of the cord blood of newborns indicated that allergen priming to a variety of milk proteins had occurred prenatally, but the relevance of this needs further study.[148]

Various milk proteins can cause an IgE-mediated reaction, which can result in hives, wheezing, asthma, and anaphylaxis. It has also been suggested that inadequate quantities of maternal IgAantibodies to food allergens may play a permissive role in the development of allergic disease in breast-fed infants.[149]

IgE-mediated milk allergy usually disappears by three years of age, but occasionally may persist into adulthood. Attempts have been made to prevent this allergic reaction in high risk, atopic babies, by placing breast-feeding

mothers on milk-free diets, or feeding the babies highly hydrolyzed formulae. Both techniques may increase babies' thresholds for sensitization, but whether such sensitization has been avoided or simply deferred is in question. It has been reported that feeding whey hydrolysate formula to atopic children during the first six months of life postponed cow's milk allergy symptoms up to the age of 12 months, but once the diets of the subjects and controls were similar the incidence of atopy in the two groups was the same.[150,151]

Although highly hydrolyzed milk formulas are regarded as less allergenic, anaphylactic reactions to them have been reported.[152,153] Criteria for labelling infant formulas as "hypoallergenic" are discussed in a position statement from the Canadian Pediatric Society, Allergy Section.[154] An extensively hydrolyzed infant formula for children with multiple food protein intolerances has been reported to be well tolerated.[155] Feeding extensively hydrolyzed cow's milk formula to atopic children during the first 14 months of life can protect against the development of cow's milk allergy up to the age of four years. It has been suggested that this might be a prevention and not just a postponement of the onset of symptoms,[156] but more research is needed to verify this.

Of concern to milk-allergic individuals is the introduction of microparticulated proteins from milk into a variety of foods to serve as fat replacers.[8] The use of milk-based edible films and coatings[157] is also of concern. Clear labelling of foods containing such products is essential.

Cross-reactivity between certain cow milk and goat milk proteins has been reported, suggesting that goat milk may not be a safe alternative to cow milk for many children with cow milk allergy.[158] Occasionally, milk-allergic children may also develop a beef protein allergy.[159]

It should be noted that lactose, a sugar in milk that is a commonly used ingredient in manufactured foods, may contain traces of casein and whey proteins, and has been reported to cause adverse reactions in individuals sensitive to milk proteins.[160]

Milk intolerance. Milk protein-induced gastroenteropathy develops in some babies fed cow's milk. It is triggered by large amounts of cow milk antigen, and may cause gastrointestinal problems such as vomiting, diarrhea, colic,[25] and insomnia.[161] Mucosal abnormalities similar to the flattened villi of celiac disease are sometimes reported in such children.[162] Such reactions are not associated with cow milk-specific IgE antibodies or with anaphylactic reactions, and are better described as food intolerance rather than food allergy. Cow milk-induced pulmonary disease called Heiner's syndrome is a rare disorder associated with serum precipitins to milk proteins.[26,163] Symptoms include failure to thrive and chronic upper and lower respiratory symptoms due to pulmonary infiltrates and pulmonary hemosiderosis.

Lactose intolerance. Another common reaction to milk is an intolerance to lactose. Lactose, a sugar unique to milk, is converted in the small intestine by an enzyme called lactase into two readily absorbed sugars called glucose and galactose.[164] If there is not enough lactase present to digest the lactose, abdominal bloating, acid diarrhea, cramping, pain, and sometimes nausea and vomiting result, especially in infants.[165] Most people with lactose intolerance can tolerate 100 to 200 mL (i.e., 5 to 10 g lactose) in a single dose.[166]

In most mammalian species there is a decline in lactase activity at weaning, resulting in reduced tolerance to milk and milk products. It is widely recognized that lactose intolerance is the norm in most adult populations of the world.[167] Lactase deficiency ranges from 0% among the Dutch, to 32% among the French, 65% among African Americans, 72% in Southern Italians, 95% in North American Indians.[164,165] In a recent study of adult and elderly Asian Americans, no significant change in lactose tolerance was noted with increasing age in adulthood.[168]

Eggs

Eggs have been found to be responsible for 25% of the DBPCFC confirmed adverse reactions in children in the United States[25] and for 40% of all food allergy reactions among children in France,[79] and can cause anaphylactic reactions.[142] The three most allergenic proteins in eggs are present in the egg white. They are ovalbumin, ovomucoid, and conalbumin (ovotransferrin),[25,169] with ovomucoid being the most important allergen in the development of egg allergy.[170] Conalbumin tends to be destroyed on heating, but ovalbumin and ovomucoid are both quite heat stable, so that cooked eggs retain much of their allergenicity.[25] The death of a two-year-old girl from anaphylaxis from egg in a hamburger roll has been reported.[15] A severe allergic response to a food containing 0.02% (200 ppm) of ovalbumin has been reported.[58] DBPCFC have confirmed that eczema in atopic babies can result from maternal intake of eggs while they are breast-feeding.[171]

The "bird-egg syndrome" describes a late onset allergy to egg proteins that develops as a result of respiratory exposure to avian proteins, e.g., bird feathers.[172] There have also been reports of allergic reactions to chicken meat without sensitization to egg protein,[173,174] and another report in which allergic reactions to chicken, quail, and turkey meat were associated with allergy to egg.[175] IgE-mediated inhalation allergy to egg white has also been reported.[176] Egg yolks contain proteins that may cross-react with egg white antigens.[25] Microparticulated egg protein, which is used in a fat replacer, could be a problem for individuals with egg sensitivity.[8,157] Like allergies to milk, severe allergic reactions to eggs are often outgrown by three years of age,[114] but a few individuals retain the allergy into adulthood.

Lysozyme, an egg derived enzyme used in cheese manufacture in some countries, has been reported to cause sensitization in one out of three of patients with egg allergy.[58,177] Lysozyme is presently not allowed as an ingredient in cheese making in Canada, but if introduced, the required common name would be egg white lysozyme.

Fish

Many varieties of fish have been reported to cause allergic reactions in sensitized individuals. The prevalence of fish allergy is not known, but it is higher in countries where people consume large amounts of fish.[178] Most individuals who are fish sensitive are atopic, and skin prick testing is often used to determine specific varieties of fish to which they react.[179] It has been shown that some fish-sensitive individuals may react to only one variety of fish, while others may react to several varieties.[180] DBPCFC to different varieties of fish are regarded as the most reliable method of confirming specific fish allergies.[179]

Severe IgE-mediated and nonimmunologic reactions can occur both as a result of ingesting fish and inhaling fish vapors developed while fish is being cooked.[181,182] Itching and hives are the most common symptoms reported, followed by respiratory problems and shock.[179] Death from fish-related anaphylaxis has been reported from eating food cooked in oil in which fish had been fried.[75] It has been predicted that more fish allergies will be reported as fish is incorporated into a wider variety of products, e.g., surimi (reformed fish) in imitation crab, pizza toppings, etc.[183]

Of the allergens identified in foods the allergen from codfish, *Gad c* I, is probably the most extensively studied. *Gad c* I belongs to the parvalbumins, a group of vertebrate muscle calcium chelating proteins. It is very stable and it appears that its allergenicity is based on its amino acid sequence and not its configuration.[179] Of interest was a report that, in rare circumstances, heat denaturation of fish created new allergenic epitopes,[184] and that allergenic proteins increased in cod during storage.[185] Also of interest is the change in the allergens in surimi, which is made from non-water soluble proteins after small fish from a variety of species are washed extensively in water. It is postulated that these proteins polymerize to form new allergenic materials different from the original fish protein. In addition, surimi may contain other allergenic ingredients including egg white.[186]

Cross-reactivity with other fish, especially hake, carp, pike, and whiting, is likely a result of similar amino acid sequences in these fish varieties.[179] It has been reported that testing for cod allergy is useful in testing for other fish allergies, since 85% of the children tested were positive for one or more of 17 different fish species.[187] Tuna does not show much cross-reactivity with other species, because of the lack of similar amino acid sequences,[179] or because of prolonged heating during processing,[142] or both. Many individuals with adverse fish reactions also report adverse reactions to certain Crustacea, especially shrimp.[179] In spite of evidence to the contrary in the literature, it has been reported that symptoms of fish allergy tend to disappear in many children by age six, possibly as a result of desensitization.[34,181] Desensitization by rush immunotherapy has been successfully used on a 39-month-old girl who was severely sensitive to fish.[188] However, the reviewer stressed that this is still a very risky technique.

Crustaceans and Shellfish

It has been estimated that 250,000 people in the United States have developed, or are at risk of developing, allergic reactions to crustaceans and mollusks.[189] Crustaceans are more frequently involved in allergy reactions than mollusks, but severe reactions to mollusks do occur.[56,187] Cross-reactivity among various species of crustaceans is high,[190] and some cross-reactivity has been found between certain crustaceans and mollusks.[187] Crustaceans commonly consumed in Canada include shrimp, prawns, lobster, crab, and crayfish. Commonly eaten shellfish include oysters, scallops, mussels, and clams.

The major allergen of brown shrimp is called *Pen a* 1 and has been identified as the muscle protein tropomyosin.[191] A sensitive ELISA has been developed to quantify *Pen a* 1.[192] Severe adverse symptoms from crustaceans and mollusks have been reported from ingestion, or from inhalation of vapors produced during cooking.[193,194]

Cereals

A variety of cereals have been implicated in both IgE-mediated allergic reactions and in gluten-induced enteropathy, with wheat being the most commonly reported.

Wheat. IgE-mediated allergies to wheat have been reported in children in the United Kingdom,[39] the United States,[45] and Finland.[195] Using immunoblotting analysis, some of the major allergens in wheat flour were found to have molecular weights in the 15, 17, and 47 kDa regions.[196] The 15 kDa wheat protein has been identified as an α-amylase inhibitor, which is capable of sensitizing both by ingestion and by inhalation.[197] There are conflicting reports of cross-reactivity among the various cereals. Some researchers have indicated strong associations between specific IgE levels to wheat flour and those of rye and barley,[198] while others have reported clinically insignificant cross-reactivity among cereal grains and grasses, and suggest that the elimination of all grains from the diet of an individual with a grain allergy is unwarranted.[199]

Of interest are reports of early sensitization of babies to cereal antigens, from breast milk[52] and through airborne exposure.[200]

Anaphylactic reactions to wheat, although not common, have been reported, and it is unclear whether this allergy will be outgrown.[19] More frequently reported is exercise-induced anaphylaxis after wheat ingestion. In one group of 19 patients with exercise-induced anaphylaxis, 12 had wheat sensitization.[201] The mechanism by which physical exertion promotes these reactions is still poorly understood.[22] In a recent study of five patients with cereal-dependent exercise-induced anaphylaxis, the allergen in question was found to be wheat gliadin and the corresponding ethanol soluble prolamins of rye, barley, and oats. Treatment with a gluten-free diet was found to eliminate the incidence of anaphylaxis.[202]

Corn. Corn is not a common allergen. In one study involving 480 DBPCFC in the United States, most of them done on children, only one had a reaction to corn.[35] However, for those individuals with hypersensitivity to corn, it can be very difficult to avoid since corn is so ubiquitous in manufactured foods in North America. One case of exercise-induced anaphylaxis to corn has been reported.[203]

Rice. Another cereal allergy of interest is an allergy to rice, which is not common in North America but has been reported in Japan. The salt soluble globulin proteins were reported to be more allergenic than glutelin proteins.[204] Further studies isolated the salt soluble rice proteins containing albumins and globulins, and found that the albumin fraction contained several proteins with molecular weights in the range of 14 to 16 kDa. It was found that these allergenic proteins have a structure similar to that of α-amylase/trypsin-inhibitors in other cereals and legumes.[205] A low incidence of rice allergy has been reported in a study from Australia and Asia.[42]

Gluten and celiac disease. A much more widely recognized adverse reaction to the specific proteins of wheat, rye, barley, and oats, which are frequently grouped under the general term "gluten," occurs among individuals with celiac disease, and a related skin condition called dermatitis herpetiformis. There is increasing evidence to support the view that both conditions are caused by T-cell mediated hypersensitivity to the storage proteins of wheat, rye, barley, and possibly oats.[206]

Wheat, rye, barley, oats, and their hybridized strains (e.g., triticale) contain storage proteins (prolamins) with peptide sequences, which trigger the destruction of the absorptive villous lining of the intestinal tract in celiac patients. The specific names of the offending prolamins are: gliadin (from wheat), hordein (from barley), secalin (from rye), and avenin (from oats). The proteins of corn (corn gluten) and of rice (including glutinous rice) are not toxic to individuals with celiac disease.[207] The safety of oats for individuals with celiac disease has been a matter of debate,[208] and research is now underway to determine long-term effects of oat consumption by individuals with celiac disease.[209]

In some countries, the incidence of celiac disease appears to be increasing,[210-212] possibly due to better diagnosis.[213] Incidence at two years of age of about 1/300 in Sweden has been reported.[210] The prevalence of celiac disease in Canada has been estimated to be 1/2000, but many researchers regard this as an underestimation.[214] The prevalence of subclinical celiac disease in Italy is estimated at 328/1000 population, and this disease is regarded as the most common life-long debilitating disease in Italy.[212]

The only treatment for celiac disease is a gluten-free diet for life. If a gluten-free diet is not followed, serious malabsorption of many nutrients occurs, including iron, folic acid, calcium, fat soluble vitamins, and protein. Untreated celiac disease also results in a significant risk of lymphoma and other malignancies including cancer of the mouth, pharynx, and oesophagus.[23,215] Several researchers have recently reported that the incidence of cancer is decreased on a strict gluten-free diet, but not on a gluten-reduced diet.[23,216,217] In an 11-year study of 210 subjects with celiac disease, it was shown that subjects who followed a strict gluten-free diet reduced their risk of developing cancer to that of the general population.[23] The results of a retrospective study of 487 patients with dermatitis herpetiformis also suggest that a strict gluten-free diet for this condition plays a protective role against lymphoma.[218]

Untreated celiac disease results in short stature in children[219] and also greatly increases the risk of osteoporosis in adults.[24,220-224] A strict gluten-free diet has been reported to remarkably improve bone mineralization in children with celiac disease and to maintain bone mass in adults.[224]

The question of whether there is a level of tolerance for gluten among individuals with celiac disease has been a daunting problem for various reasons, including the lack of a suitable animal model, and the difficulty of doing repeated intestinal biopsies on patients to evaluate gluten response. Several studies have reported that even small amounts of dietary gluten cause pathogenic changes to the mucosal cells, even if there are no obvious clinical symptoms or detectable changes in the serum levels of antigliadin antibodies.[225,226] Similar conclusions were drawn from a study of children with celiac disease on gluten-free diets who were challenged with gliadin (daily dose of 100 mg or 500 mg). The authors concluded that chronic ingestion of small amounts of gluten causes dose-dependent damage to the mucosa of the small intestine in children.[227] For these reasons, many researchers now stress the need for a strict gluten-free diet for life for celiac patients.[10,217,222,225-227]

In 1995 the Canadian *Food and Drug Regulations* described a gluten-free food as one that does not contain

wheat, including spelt and kamut, or oats, barley, rye, or triticale, or any part thereof. By contrast, the Codex Alimentarius standard for gluten-free foods allows a maximum of 200 ppm of gluten to be present. The validity of this standard is now under review.

Unlike Canada, the United States, Australia, Italy, and several European countries allow the use of wheat starch as a basis for "gluten-free" baked goods. Studies have shown that wheat-based "gluten-free" products can cause persistent symptoms in many celiac patients using such products,[217,228] because it is very difficult to completely remove all traces of gluten during the manufacture of wheat starch.[229]

Of concern to individuals with celiac disease were gluten-based coatings for fruits and vegetables being developed in Europe.[211] Because of the serious consequences of small amounts of gluten in the diet of celiac patients, it is essential that all gluten sources be completely labelled.

Sulphites

The earliest report of sulphur dioxide causing asthma was in a child who ate dried fruit preserved with sulphur dioxide. Since then, more than 1000 cases of sulphite-related reactions to foods including 20 deaths, have been reported in the United States. In Canada, more than 100 sulphite-related reactions and at least one death have been reported.[26] A few individuals appear to have an IgE-mediated sensitivity to sulphite,[26] but a deficiency of sulphite oxidase, an enzyme responsible for oxidizing sulphite (SO_3) to inactive sulphate (SO_4), and hyperreactivity to inhaled sulphur dioxide are thought to be the causes in most sulphite-sensitive individuals.[230] There have been reports of individuals hypersensitive to sulphites reacting to levels as low as 1 ppm by inhalation,[231] although levels below 10 ppm in a food matrix are believed to be tolerated by most sulphite-sensitive individuals.

Reactions vary depending on the form of the sulphite, the amount present, and the mechanism of sulphite sensitivity.[232] They range in severity from nausea, abdominal pain, diarrhea, to seizures, asthma, and anaphylactic shock.[233] Adverse reactions to sulphite in non-asthmatics are extremely rare, but it has been estimated that almost 4% of all asthmatic patients are at risk of a reaction to sulphites.[234,235] A recent report of asthma induced by pickled onions suggested that both the sulphite and the pH level were responsible for the asthmatic reactions in the study group.[236]

The use of sulphites in fresh and processed foods has been limited by regulation in the United States and other countries.[237] Regulations limiting sulphites in foods in Canada are currently in place and the publication of additional labelling regulations is anticipated in the near future.

Other Foods

Fruits and vegetables. Fruits and fruit juices, including orange, apple, and grape have been reported to cause skin rashes and diarrhea in young children. These reactions appear to be non-IgE-mediated and are often outgrown.[35] One study from Israel reported that among 112 patients with a history of immediate reactions after ingesting certain fruits and vegetables, their symptoms had started after 10 years of age.[238] It is possible that these reactions were the result of the oral allergy syndrome.

i) Oral Allergy Syndrome: Many IgE-mediated reactions to fruits, vegetables, and nuts do occur, and are frequently associated with pollen sensitivity. Such reactions occur more often among individuals allergic to birch pollen, but can also occur in individuals who are allergic to grass, ragweed, or mugwort pollens.[239,240] The name given to such reactions is the "oral allergy syndrome." Mugwort is a common plant in Europe and ragweed is more common in North America. The allergens in these plant pollens are profilins, which are proteins involved in disease resistance and fertilization in the plant, and which have structural similarities to those in a wide variety of fruits, vegetables, and nuts. Because of their wide distribution in a variety of plants they are sometimes called pan-allergens.[241] Allergic reactions associated with oral allergy syndrome can occur at any time of year, but are often worse during the pollen season involved. Unlike individuals with other food allergies, oral allergy patients are often allergic to a large number of foods, and the syndrome is usually lifelong.

The allergens contained in fruits and vegetables tend to be heat labile, therefore symptoms associated with the oral allergy syndrome usually occur only with raw foods.[242] Cooked, canned, and microwaved fruits and vegetables are usually well tolerated,[243] except for cooked celery, which has been reported to cause sometimes severe allergic reactions,[244] and rarely for cooked potato.[245] It is important to note that nuts also tend to retain their allergenicity after cooking. It has been reported that freshly picked fruits are sometimes less allergenic than they are after storage, and it has been reported that peach skins are more allergic than the flesh.[246] Further studies may clarify the reasons for such anomalies.

The oral allergy syndrome tends to occur in older children and adults, and is almost always preceded by hay fever. The symptoms usually occur within minutes of contact with the offending food, but delayed reactions sometimes occur.[239] The most common symptoms are usually mild and can include itching and burning of the lips, mouth and throat, watery itching eyes, runny nose, and sneezing. More serious symptoms may include hives, swelling of the mouth and pharynx, and in severe cases, bronchial asthma,

vomiting, diarrhea, generalized hives, and occasionally anaphylactic shock.[247] Peeling or touching the foods involved may sometimes cause itching, swelling or rash where the juice touches the skin, necessitating the use of gloves during their preparation.[239,248,249]

Table II summarizes the most common foods associated with birch pollen allergy, and Table III summarizes the most common foods associated with grass, ragweed, and mugwort pollen allergy. Several similarities among the foods associated with the various pollen allergies will be noted.

Anaphylactic reactions to a variety of fruits and vegetables have been reported including kiwi fruit,[250,251] white potato,[252] celery,[253] parsley,[244] beans,[254] cumin,[255] hazelnut,[241] and garlic.[256] An excellent review entitled the *Oral Allergy Syndrome* has been published.[257]

ii) Favism: Adverse reactions to foods are sometimes genetic in nature. An example of this is favism, a disease which develops in predisposed individuals when they ingest broad beans or fava beans or inhale the flower pollen. The condition is not IgE-mediated, and is therefore regarded as a food intolerance. The condition is a result of a deficiency of glucose-6-phosphate dehydrogenase in the red blood cells, and of reduced glutathione, which is needed for red blood cell integrity. Fava beans contain substances that oxidize glutathione, which results in acute hemolytic anemia. Areas of the world most affected by this disease are the Mediterranean, Asia, Middle East, and Formosa. In the United States, favism is reported to affect 1% to 2% of Caucasian Americans and 10% to 15% African Americans.[258]

Chocolate. Historically, chocolate was believed to be a major allergenic food. However proven allergic reactions to chocolate are very rare.[259] Of 274 subjects in DBPCFC studies, only 8 were reported to have a reaction to chocolate.[25]

Phenylethylamine, a naturally occurring pharmacologic agent in chocolate which can mimic allergic reactions may be part of the explanation for so many suspected allergic reactions to chocolate.[260] Also, commercially made chocolate products often contain other allergenic substances such as nuts, milk, soy, etc. It is essential, therefore, that such products be completely and accurately labelled.

Monosodium glutamate (MSG). MSG is the sodium salt of glutamic acid. Because of its wide use as a flavor enhancer in Chinese food, the name "Chinese restaurant syndrome" has been used in the past to describe the reaction to this substance in sensitive individuals. MSG symptom complex has been suggested as a better name for this reaction.[261] This syndrome may be characterized by headache, muscle tightness, numbness and tingling, flushing, and general weakness.[261] There is no evidence that free glutamates present naturally in foods have a different effect on sensitive individuals than do manufactured salts of glutamic acid, such as monosodium glutamate. The cause of the MSG symptom complex is not understood, but it is not an IgE-mediated process.[16]

In a DBPCFC random study of individuals with a history of sensitivity to MSG, it was reported that the majority of individuals did not react. In those who did, the reactions were mild and the threshold dose reported was 2.5 g.[261] A major report on MSG by the U.S. Food and Drug Administration indicated that certain healthy individuals may respond, generally within one hour of exposure, to an oral intake of MSG of more than 3 g in the absence of food.[262] This report also mentioned that there have been no scientific reports of adverse effects from ingesting protein hydrolysates from microbial, vegetable, or animal origin. A carefully controlled study of 12 subjects with clinically documented asthma and a perceived MSG-induced asthma recently reported that no asthma symptoms developed in these patients after doses of 1 g MSG and 5 g MSG, given in a single dose after an overnight fast.[263]

Canada's *Food and Drug Regulations* require glutamic acid and its salts, which include monosodium glutamate, to be declared by name as ingredients on the food label, both when they are added as ingredients and when they are present as components in food mixtures.

Other Food-Related Concerns

Latex allergy. Immediate type I hypersensitivities to natural rubber latex are not uncommon. They are caused by water soluble proteins in latex sap.[264] Two cases of severe allergic reactions to latex from eating fast food prepared by handlers wearing latex gloves have been reported.[265] In addition many cross-reactivities between latex and banana, avocado, papaya, kiwi, peach, chestnut, and peanut have been reported.[266-269] Although these foods are from different botanical families, they appear to have common epitopes. Cross-reactivites appear to be independent of the molecular weight of the allergen.[264] Further study of these latex-fruit cross-activities is needed.[270]

α-amylase. α-amylase, a starch-cleaving enzyme added to wheat flour to improve its baking quality, is a major allergen for bakery workers, causing both allergic reactions and asthma in hypersensitive individuals. Heating reduces but does not destroy the allergenic activity of this enzyme.[271] Since α-amylase can be present in fruits, vegetables, sugar, honey, etc., it should be considered when diagnosing food allergy.[272]

Table II Most common foods associated with birch pollen allergy	
Food Type	**Specific Foods Involved**
Fruits	kiwi (**apple family**): apple, pear (**plum family**): plum, prune, peach, nectarine, apricot, cherry
Vegetables	(**parsley family**): celery, carrot, parsnips, parsley, dill, anise, cumin, coriander, caraway, fennel (**potato family**): potato, tomato, green pepper (**legumes**): lentils, peas, beans, peanut
Nuts	hazelnut, walnut, almond
Seeds	sunflower

Novel foods derived through genetic engineering. In a study involving a gene transfer from Brazil nut to soybeans, the researchers concluded that the genetically modified soybeans would be allergenic to individuals with Brazil nut allergy,[273] and the research was discontinued. Researchers have also expressed concern about the possibility of introducing or creating new allergenic epitopes when genetic modifications are being made to a food. In its evaluation of novel foods, Health Canada always takes their potential allergenicity into consideration.

The labelling of such foods is being widely discussed internationally. At a multi-sectorial workshop in Ottawa in November, 1994, it was agreed that when genes from a food known to cause severe adverse reactions are transferred into another food, the resulting food should be labelled to identify this.[274] Until adequate testing for potential allergens is available, many researchers have concluded that strict labelling must be mandatory.[275]

CANADA'S PRESENT LABELLING REGULATIONS

Canada's *Food and Drug Regulations* presently exempt certain ingredients and components (ingredients of ingredients) from being declared on food labels. In addition, they permit the use of certain class names and unspecific common names on food labels. Following is a discussion of the impact of these regulations on foods known to cause severe adverse reactions in Canadians.

Foods Presently Exempt From Ingredient and Component Declarations

Tables IV and V list ingredients and components that are presently exempt from being declared on food labels, under Canada's present *Food and Drug Regulations*. If a declaration of the foods known to cause adverse reactions were to be made mandatory, or if exemptions from component declarations for these foods were to be revoked, the typical components listed in these tables would have to be identified by name on food labels. Such ingredient declarations would provide more complete and accurate label information to Canadians with food hypersensitivities. Such labelling requirements would also make Canadian ingredient labelling requirements more closely harmonized with those of the United States.

Table III Most common foods associated with other pollen allergies	
Pollen Type	**Specific Foods Involved**
Ragweed	(**gourd family**): watermelon, cantaloupe, honeydew, zucchini, cucumber banana
Grass	melon, watermelon, tomato, orange, kiwi
Mugwort	apple, celery, carrot, watermelon, melon

Class Names

"Flavor," "color," "seasoning," and "spices" are among a group of class names presently allowed on food labels by the *Food and Drug Regulations*. Such foods, particularly seasonings and flavors, often contain ingredients such as wheat, milk, egg derivatives, etc. (Table III). Administratively, the use of the class name "seasoning" is permitted if a seasoning mixture is added to a food at 2% or less of the weight of the final product. When the class name is used, the individual ingredients of the seasoning are not required to be identified on the label. Although such names may give flexibility to the manufacturer, they severely limit the choice of foods that can be purchased by individuals with adverse reactions, since many avoid all foods identifying only "seasoning" or "flavoring" on the label because of their desire to be safe rather than sorry.

Unspecific Common Names

Hydrolyzed plant proteins. The term "hydrolyzed plant protein" is presently allowed as a common name in the ingredient list for all hydrolyzed plant proteins, except for those manufactured by enzymatic hydrolysis which are required to include the plant source, e.g., "hydrolyzed soy protein." Hydrolyzed plant proteins in Canada are most commonly from soy, wheat, and corn, but they can also be made from peanut protein. The safety of such proteins for individuals with food sensitivities is in question. Testing the allergenicity of some of the hydrolyzed proteins presently available in Canada cannot ensure the safety of such products coming from abroad. Because the plant source of these proteins is not identified on food labels, many people with sensitivities to soy, wheat, and peanut tend to avoid all foods listing "hydrolyzed plant protein" on the label. This is unnecessarily restrictive for individuals with food allergies since these products are so widely used as flavoring agents.

Also of concern are partially hydrolyzed plant proteins, which are now being manufactured for addition to foods for both their flavor and texture modifying

Table IV Examples of food ingredients presently exempt from a component declaration under the *Food and Drug Regulations* [B.01.009(1)], and typical components

Ingredients exempt from a component declaration	Typical components exempt from being declared
margarine	milk ingredients
bread	up to 5% non-wheat flour (e.g., pea, soy, etc.)
baking powder	starch
glucose, glucose solids, glucose syrup icing sugar	sulphurous acid or its salts, e.g., sulphites starch
relish	flour or starch
prepared meat, fish, poultry if less than 10% of an unstandardized food	"fillers" may contain: flour, starch, gluten, milk, soy, etc. "binders" may contain: milk, egg, seasonings, etc.

characteristics, and which do retain their antigenicity. If the plant source were included in the common name of all forms of hydrolyzed and partially hydrolyzed plant proteins, individuals with food sensitivities could select from a much wider variety of prepackaged foods. In addition this would bring Canadian labelling requirements into closer harmony with those of the United States,[276] which now require a declaration of the plant source in the common name of all hydrolyzed plant proteins.

Modified starch. Modified starches are usually from corn, but they may be made from wheat and other starches. It is very difficult to completely remove all traces of potentially allergenic protein from wheat during the manufacture of food grade starch,[229] and for this reason wheat starch is not allowed in gluten-free foods in Canada. Most individuals with sensitivities to wheat avoid all foods containing "modified starch" because the plant source is not identified. Specific labelling would allow consumers with hypersensitivities the necessary information to make safe choices from a wider choice of prepackaged foods.

Unexpected or Hidden Sources of Foods Causing Adverse Reactions

It is widely recognized that full disclosure of all ingredients in prepackaged foods is desirable for consumers, especially those with food sensitivities. In addition to the impact of regulatory component exemptions on the labelling of foods, there are many reasons for incomplete or inaccurate ingredient listings on prepackaged foods. These include:

- carry-over of product through incomplete cleaning of food contact surfaces and utensils, sometimes because of poor equipment design;

Table V Food preparations used as ingredients which are presently exempted from a component declaration under the *Food and Drug Regulations* [B.01.009(2)], with examples of typical components

Mixtures exempt from an ingredient and component declaration	Typical components exempt from being declared
food color preparations	soy lecithin
natural and artificial flavoring preparations	malt wheat starch, wheat flour, wheat gluten enzyme-modified cheeses
spice mixtures	wheat flour, wheat starch sesame seeds
seasoning or herb mixtures	if <2% of product: HPsauce, Worcestershire sauce, soy sauce, ketchup, mustard, cheese powder skim milk powder wheat flour, wheat starch peanuts, tree nuts, seeds, fish, etc.
vitamin preparations	soybean oil wheat starch
food additive preparations	wheat starch wheat flour
compressed dry, active, or instant yeast preparations	starch

- inappropriate use of rework (recycled processed food) containing allergenic ingredients;
- ingredient changes, substitutions, or additions not reflected on the label;
- incorrect labels put onto products;
- incorrect or incomplete list of ingredients;
- unknown ingredients in raw materials;
- misrepresentation of common names to describe products/ingredients (e.g., mandelonas for reformed, reflavored peanut);
- labelling exemptions under the *Food and Drug Regulations.*

Numerous incidents of adverse reactions to hidden or unexpected foods, including fatal reactions, have been reported in the scientific literature and by Health Canada and Canadian Food Inspection Agency inspectors. Table VI summarizes some of the hidden food allergens reported in the scientific literature (which are identified by the source), and by our food inspectors. Also included in this chart are some alternative names that consumers with food hypersensitivities should be aware of for such foods.

Many of the severe reactions to foods reported in this table resulted from unlabelled foods eaten away from home, at school, in restaurants, etc., and some resulted from mislabelled foods and cross-contamination. A recent paper discusses hidden allergens primarily in processed foods.[277]

Table VI Hidden sources and alternative names of foods causing adverse reactions recently reported in the scientific literature and by Canadian government inspection agencies

Food	Alternative Names or Components	Hidden Sources
peanuts	goober nuts* goober peas* ground nuts* mandelonas* arachis oil (*These names are not allowed on food labels in Canada)	• almond icing[283] • deflavored, reflavored sold as walnuts, almonds, etc.[88] • chili[51] • peanut oil[94] • baby formula[91] • vegetable burger[284] • flavoring in dry soup mix[285] • chocolate from Europe • peanut oil in enrichment vitamins added to milk • gravy • egg rolls • hazelnut paste
tree nuts	nuts	• pesto sauce • coffee grinders used to grind nut-flavored coffees
milk	casein sodium caseinate lactalbumin lactoglobulin whey curds lactose	• ice cream in sorbet[286] • lactose in seasoning and lactalbumin as natural flavor[25] • casein and whey protein in lactose[287] • fat substitute from milk[8] • seasoned potato chips[287] • milk in "non-dairy" hot dog and bologna[57] • milk glaze on bakery products
egg	albumin ovalbumin ovomucoid lysozyme	• fat substitute from egg[8] • glazes on baked goods • lysozyme in cheese
soy	lecithin	• soy protein in soy lecithin and margarine[133] • milled corn[288] • soup stock cubes and Spanish sausage[289] • in bread crumbs • canned tuna (in broth)
fish	surimi kamaboko	• surimi in pizza[179] • anchovies in Worcestershire sauce
wheat	spelt kamut	• binders and fillers in meat, poultry and fish products • icing sugar • baking powder • paprika • seasonings • wheat germ in black pepper

National Allergy Alerts

In 1991, to help overcome the possible consequences of incomplete or inaccurate labelling of foods known to cause adverse reactions, the Health Protection Branch (HPB) of Health Canada, instituted an Allergy Alert Program. From 1991 to 1996, 49 allergy alerts were issued, based on hidden allergens identified by consumers, industry, and federal inspectors. In September 1996, the responsibility for food recalls and national allergy alerts was transferred from Health Canada to Agriculture and Agri-Food Canada, and subsequently on April 1, 1997, to the newly formed Canadian Food Inspection Agency (CFIA). From September 1, 1997 until August 31, 1998, the Agency has been involved in 229 food recalls, of which 60% were allergy related. During this one-year period, there were 53 national allergy alerts issued. The allergens involved were peanut (25), soy (11), egg (9), milk (6), tree nuts (5), sesame seed (1), and sulphite (1), with five alerts involving more than one undeclared allergen.

In addition to government initiatives in the area of adverse reactions to foods, many Canadian food manufacturers have also taken a lead role in educating food

handlers in the prevention of cross-contamination of foods, and the need for accurate labelling.[3,278] Vigilance on the part of food manufacturers to help prevent adverse reactions to foods is essential.[279]

Precautionary Labelling

In 1994, the HPB of Health Canada established a policy allowing a "may contain" statement regarding the possible presence of allergens in foods, to be placed at the end of the list of ingredients on a food label, for example "may contain peanuts" and "may contain traces of peanuts." The policy indicated that such statements were voluntary and should not be used in lieu of adherence to "Good Manufacturing Practices." However, concern is now being voiced by many consumers about the proliferation of warning statements on food labels. Unnecessary use of such statements will greatly reduce the variety of prepared foods available for consumers with food hypersensitivities. It is essential, therefore, that such statements are true, that they reflect an increased risk to individuals with food allergies, and that manufacturers use such statements judiciously and only as a last option when it is impossible to assure the absence of allergens in a food product.

Recommendations

1. The following foods and their derivatives, when added as *ingredients or components of ingredients* to prepackaged foods, should always be declared on food labels by their specific common names: *peanuts*, *tree nuts* (almonds, Brazil nuts, cashews, hazelnuts [filberts] macadamia nuts, pecans, pine nuts, pistachios, walnuts), *sesame seeds*, *milk*, *eggs*, *fish*, *Crustacea* (e.g., crab, crayfish, lobster, shrimp), and *shellfish* (e.g., clams, mussels, oysters, scallops), *soy, wheat, sulphites*.

2. The plant species should be identified in the common names on food labels of all forms of hydrolyzed plant proteins and starches and lecithin (e.g., hydrolyzed soy protein, modified wheat starch, soy lecithin).

3. Food manufacturers, importers, distributors, and food service establishments should develop an Allergen Prevention Plan to manage allergy risks.

Conclusion

Accurate labelling of ingredients causing adverse reactions in sensitive individuals is essential both in Canada and internationally. This document has identified a list of the most common foods causing serious IgE-mediated reactions. It has also identified the need for accurate labelling of those foods known to cause serious chronic disease, such as celiac disease. The development of international criteria for accurate labelling of foods causing either severe immediate reactions or serious chronic disease will enable all individuals with food sensitivities to choose a safer and wider variety of prepared foods in the marketplace.

Adverse reactions to foods occur for a variety of reasons, including incomplete labelling, and cross-contamination during transport, storage, and manufacture. In other cases they result from unlabelled foods consumed away from home. Therefore, increased safety of foods for sensitive individuals will only be possible with a concerted effort by food manufacturers, the food service industry, government regulators, and consumers. Those individuals with severe adverse reactions to certain foods must be vigilant, read labels carefully, and always avoid any questionable foods. The old but revised adage remains true for all: a milligram of prevention is worth a kilogram of cure.❑

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