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Is it allergy?

Legumes, Nuts & Seeds

Allergy – Which allergens?

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SCIENTIFIC

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Contents

Legume, nut and seed allergens

This reference book describes the 42 allergens categorized as Legumes, Nuts and Seeds available as ImmunoCAP® allergens for *in vitro* testing. A number of allergens customarily listed in these categories do not in the strict sense fulfil the definition of that category either in the botanical sense or because they may easily fit into two categories. For example, Lupin seed could appear to belong to the seed category, and here is preferentially categorised as a legume. Whether Peanut is a nut or a legume may not always be immediately obvious, in particular as Peanut has characteristics of both. A number of foods classified here, have pollen counterparts that are recognized as aeroallergens resulting in asthma and rhinoconjuctivitis, *e.g.*, Wheat and Rye.

Legumes

Both grain legumes and nuts consist of a simple dry fruit carried inside a pod or shell. In the strict botanical use of the term, a nut will usually have only one seed and at most two compared to legumes which contain multiple seeds. Most legumes are dehiscent, opening naturally along a seam on two sides, compared to a true nut that is always indehiscent, *i.e.*, does not open on its own. Legumes often contain seeds attached to their pods unlike a true nut which is never attached to the ovary wall. Peanut, classified as a legume, clearly has features of both nuts and legumes but has overriding legume characteristics, *e.g.*, its high protein yield and the capacity to replenish nitrogen in the soil.

The legumes are members of the *Fabaceae* (*Leguminosae*) botanical family. The principal unifying feature of the family is the fruit, a pod, technically known as a Legume. The *Fabaceae* is a very large family consisting of 650 genera and over 18,000 species. The family is often divided into three sub-families: *Papilionoideae*, *Caesalpinioideae* and *Mimosoideae*. These sub-families are sometimes recognised as three separate families: *Papilionaceae*, *Caesalpiniaceae* and *Mimosaceae*.

The *Papilionoideae* contains most of the important leguminous crop species such as the Soya Bean (*Glycine max*), Common Pea (*Pisum sativum*), Chickpea (*Cicer arietinum*), French Bean (*Phaseolus vulgaris*), Lentil (*Lens culinaris*) and Peanut (*Arachis hypogaea*). A legume is a simple dry fruit which develops from a simple carpel and usually opens along a seam (dehisces) on two sides. Peanut is an indehiscent legume.

The majority of the *Caesalpinioideae* are tropical or subtropical trees and shrubs. The majority of the *Mimosoideae* are tropical or subtropical trees and shrubs, of which the genera *Acacia* and *Mimosa* have species that are extremely important economically, *e.g.*, bark of the Golden Wattle (*Acacia pycnantha*) and *Acacia Senegal* which yields commercial gum arabic which is used in a wide range of industrial processes.

The legumes consist of the grain and forage legumes. More than forty species and countless varieties of grain legumes are cultivated throughout the world. The legume family is characterised by flowers that have five petals (papilionaceous flower with a butterfly form), a superior ovary that ripens to form a fruit, the specialised pod which contains seeds, and the ability to use atmospheric nitrogen to produce their own protein compounds, as a result of the symbiosis with nitrogen-fixing bacteria within organs known as nodules developed on the plant roots, for nearly all of its members. Unlike other cultivated plants, legume crops do not need nitrogen fertilisation for optimal growth in general.

The “forage” legumes are customarily grown for whole crop use for animal feed or for industrial purposes. For animal feed, the crop may be grown for grazing or for the production of silage or hay. Alfalfa (*Lucerne*) is an example of a forage legume. Conversely, “grain” legumes are cultivated primarily for their seeds which are rich in protein and energy and therefore used for human consumption or animal feed. The

grain legumes are commercially termed "pulses", but exclude the "leguminous oilseeds" that are used primarily for their high oil content. Soybean is an example of this group.

Legume species may preferable thrive in temperate climates and other prefer tropical regions. The major grain legumes grown include species belong to a number of tribes. For example, Pea (*Pisum sativum*) and Lentil (*Lens culinaris*), which are members of the *Fabeae* tribe. The tribe *Phaseoleae*, include Soybean (*Glycine max*) and White bean (*Phaseolus vulgaris*). Chickpea (or Garbanzo bean) (*Cicer arietinum*), a member of the *Cicereae* tribe, is a very important grain in the Spanish diet. Lupin seed (tribe *Genisteae*), is preferentially classified as a legume. Of the legumes, Soybean is the most important grain crop with around 185 million tonnes being produced, grown primarily in the USA, Brazil, Argentina, Paraguay and Uraguay. The world production of grain legumes other than Soybeans amounts to approximately 57 million tonnes.

Individuals may become sensitized to the legumes as a result from inhalation of aerosolized proteins from the cooking of the fruit/seed/grain of the plant, from occupational contact with the dust or actual fruit/seed/grain, or following its ingestion. Respiratory allergy as a result of inhalation of the pollen of the plant, *e.g.*, Wheat (Cultivated Wheat g15), is discussed in the reference book, ImmunoCAP® Grass pollens in this series.

Nuts

Nut is a general term for the dry seed or simple dry fruit of some plants carried inside a pod or shell (ovary wall) which becomes very hard (stony or woody) at maturity, and where the seed remains unattached or unfused with the ovary wall. In the strict botanical use of the term, a nut will usually have only one seed and at most it will have two. A true nut is always indehiscent, meaning it won't open on its own at maturity and a true nut is never attached to the ovary wall. While a wide variety of dried seeds and fruits are called nuts, only a certain number of them are considered by biologists to be true nuts. Nuts are an important source of nutrition for both humans and wildlife. A nut is the seed of a tree. When we eat the soft layer, we call it a fruit. When we eat the seed we call it a nut. A nut is a seed, but a seed is not necessarily a nut.

True nuts may be edible or inedible; common examples are Acorn, Beechnut, Chestnut, and Hazel nut. Fruits or seeds that are incorrectly and popularly termed nut include Almond and Coconut which are actually drupes with the fleshy outer layer removed. Brazil nut are seeds contained in capsules. Traditionally a distinction has been made between Peanut and Tree nuts. Peanut is actually a legume, belonging to the family *Fabaceae*. In common parlance, the culinary definition of a nut may carry more weight than the botanical definition. In culinary terms, a nut is any large seed which is used in food and comes from a shell. This group includes drupes, fruit that contain a hard pit, *e.g.*, Almond and Coconut, seeds which are not nuts, such as Cashew and Peanut.

True nuts are produced, for example, by some plants – families of the order *Fagales*:

- Family *Juglandaceae*: *e.g.*, Walnut, Pecan nut
- Family *Fagaceae*: *e.g.*, Chestnut
- Family *Betulaceae*:, *e.g.*, Hazel nut

Some fruits and seeds that are nuts in the culinary sense, but not in the botanical sense:

- Almond is the edible seed of a drupe – the leathery "flesh" is removed at harvest
- Brazil nut is the seed from a capsule
- Cashew nut is a seed
- Coconut is a dry, fibrous drupe
- Macadamia nut is a creamy white kernel
- Peanut is a legume and a seed
- Pine nut is the seed of several species of Pine
- Pistachio nut is the seed of a thin-shelled drupe

Seeds

A seed is a small embryonic plant of a seed plant before germination enclosed in a covering called the seed coat, usually with some stored food. It is the product of the ripened ovule of gymnosperm and angiosperm plants which occurs after fertilization and some growth within the mother plant. The seeds listed here are "edible" seeds. Many seeds are edible and the majority of human calories come from seeds, especially from cereals such as Wheat and Rice. Seeds also provide cooking oils, beverages and spices. Edible seeds contain storage proteins which may be found in the embryo or endosperm and differ in their amino acid content and physical properties. For example Wheat gluten, important in providing the elastic property to bread dough, is strictly an endosperm protein. Of course, seeds are used to propagate many crops. Seeds are also eaten by animals, fed to livestock and used as birdseed.

Pine nuts suggest classification as nuts, but are in fact the edible seeds of Pines (family *Pinaceae*, genus *Pinus*).

Further reading

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Legume, nut and seed ImmunoCAP® Allergens available for IgE antibody testing

f20	Almond (*Amygdalus communis*)
f6	Barley (*Hordeum vulgare*)
f310	Blue vetch (*Lathyrus sativus*)
f18	Brazil nut (*Bertholletia excelsa*)
f11	Buckwheat (*Fagopyrum esculentum*)
f202	Cashew nut (*Anacardium occidentale*)
f309	Chick pea (*Cicer arietinus*)
f36	Coconut (*Cocos nucifera*)
f55	Common millet (*Panicum milliaceum*)
f305	Fenugreek (*Trigonella foenum-graecum*)
f56	Foxtail millet (*Setaria italica*)
f79	Gluten (from *Triticum aestivum*)
f315	Green bean (*Phaseolus vulgaris*)
f17	Hazel nut (*Corylus avellana*)
f57	Japanese millet (*Echinochloa crus-galli*)
f235	Lentil (*Lens esculenta*)
f182	Lima bean (*Phaseolus lunatus*)
f333	Linseed (*Linum usitatissimum*)
f335	Lupin seed (*Lupinus albus*)
f345	Macadamia nut (*Macadamia spp.*)
f8	Maize, Corn (*Zea mays*)
f7	Oat (*Avena sativa*)
f12	Pea (*Pisum sativum*)
f13	Peanut (*Arachis hypogaea*)
f201	Pecan nut (*Carya illinoensis*)
f253	Pine nut, pignoles (*Pinus edulis*)
f203	Pistachio (*Pistacia vera*)
f224	Poppy seed (*Papaver somniferum*)
f226	Pumpkin seed (*Cucurbita pepo*)
f347	Quinoa (*Chenopodium quinoa*)
f316	Rape seed (*Brassica napus*)
f287	Red kidney bean (*Phaseolus vulgaris*)
f9	Rice (*Oryza sativa*)
f5	Rye (*Secale cereale*)
f10	Sesame seed (*Sesamum indicum*)
f14	Soybean (*Glycine max*)
f124	Spelt wheat (*Triticum spelta*)
f227	Sugar-beet seed (*Beta vulgaris*)
f299	Sweet chestnut (*Castanea sativa*)
f256	Walnut (*Juglans spp.*)
f4	Wheat (*Triticum aestivum*)
f15	White bean (*Phaseolus vulgaris*)
Mixes:	**fx1**, **fx3**, **fx5**, **fx8**, **fx9**, **f11** **fx12**, **fx13**, **fx18**, **fx20**, **fx22**, **fx24**, **fx25**, **fx26**, **fx27**, **fx28**

Amygdalus communis

Family: *Rosaceae*

Genus: *Prunus*

Subgenus: *Amygdalus*

Common names: Almond, Sweet Almond, Bitter Almond

Synonymes: *A. dulcis*, *Prunus amygdalus* and *P. dulcis*

Source material: Shelled almonds

The fruit and seeds of several other plants are known as Almonds. The seeds of the African shrub *Brabeium stellatifolium* are known as African Almonds. Country Almonds is a name given to the fruit of the East Indian tree *Terminalia Catappa*. The fruit of *Canarium commune* is known as Java Almonds

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Allergen Exposure

Geographical distribution

The Almond is the fruit of a vigorous, deep-rooted deciduous small tree belonging to the Rose family, which grows best in areas with dry, warm summers. The plant is believed to be a native of northern Africa and the Middle East. It occurs wild in Sicily and Greece and is extensively cultivated in northern Africa, southern Europe, Australia and the warmer parts of the United States, particularly California.

The fruit is a drupe or kernel stone fruit, resembling the Peach in its general structural characteristics. It is, however, much smaller, measuring about 4 cm in length. As in the Peach, the outer portion of the fruit coat (sarcocarp) is fleshy, while the inner portion (endocarp or putamen) is hard and encloses the kernel or seed, to which the term Almond is commonly applied.

Almonds come in many varieties, but the 2 major, universally recognised ones are the Sweet (*Prunus amygdalus var. dulcis*) and the Bitter (*Prunus amygdalus var. amara*). They appear very similar but are different in chemistry. In the Bitter variety, substantial amounts of amygdalin (or "laetrile"), containing hydrocyanic (or "prussic") acid, are found. The Bitter almond is banned from retail sale in the US because of the toxicity of unprocessed amygdalin. Only Sweet almonds are readily edible.

Environment

Almonds have always been an important ingredient in Arabic dishes and Indian curries. Sweet almonds (fresh, blanched, roasted, candied, and smoked; whole, sliced, chopped, and in paste form) are readily available in markets and are used in a variety of recipes, especially for sweets and confectionery. Heat-processed Bitter almonds are used to flavour extracts, flavourings, liqueurs and syrups. The purified fixed oil from both varieties of Almonds has food uses, particularly as a condiment. Almonds are a nutritional powerhouse, packed with calcium, fibre, folic acid, magnesium, potassium, riboflavin and vitamin E.

Medicinally, externally applied Almond oil is an emollient; taken internally, a laxative, nutritional substitute and supplement (particularly in cases of diabetes), and a remedy for nervous system disorders such as whooping cough and spasmodic troubles.

Almond oil and paste often feature in cosmetics and toiletries.

Unexpected exposure

See under Environment.

Allergens

A number of allergens of various molecular weights have been isolated: 12, 30, 37, 45, 50, and 62 kDa proteins. Several of these proteins were shown to be similar to a 7S globulin and a 2S albumin (1-2). Two allergens isolated were reported to be major allergens - 1 heat-labile and the other heat-stable. The Almond major protein (AMP or amandin), the primary storage protein in Almonds, is the major allergen recognised by Almond-allergic patients and is probably the 2S albumin identified previously and shown to be a heat-stabile allergen (3). The antigenicity of processed Almond proteins has been shown to be very stable when compared with that of the unprocessed counterpart (4).

To date, the following allergens have been characterised:

Pru du 2S Albumin, a 2S albumin (1).

Pru du Conglutin, a conglutin (1).

Pru du LPT, a lipid transfer protein. (5-7).

Pru du Amandin, a 360 kDa hexameric protein, an 11S legumin-like protein (8-9).

Pru du 4, a profilin (10-12).

Pru du 5, an acid ribosomal protein P2 (11,13).

Amandin is a legumin-type protein and is composed of 2 major types of polypeptides, with estimated molecular weights of 42-46 and 20-22 kDa, linked via disulfide bonds. Amandin is not a glycoprotein (7).

Pru du 4, a profilin, is a minor allergen: 6 of 18 patient sera (33%) were shown to react with the recombinant Pru du 4 protein, and 8 of 18 (44%) reacted with the native Pru du 4. More than 1 native Almond profilin isoform was isolated (9).

Potential cross-reactivity

An extensive cross-reactivity among the different members of the family, and in particular of the genus, could be expected (14). Potential clinical allergy to other *Rosaceae* should not be overlooked. If the reported reaction is confirmed, current tolerance to other *Rosaceae* should be precisely established, unless there has been ingestion without symptoms after the reaction (15).

A major Almond allergen, a 2S albumin, can be expected to result in cross-reactions with other foods containing this protein, e.g., Walnut, Sunflower seed and Peanut (1,16-17). Ara h 2, a major Peanut allergen, is a conglutin /2S albumin. In a study evaluating serum from Peanut-allergic patients, Ara h 2 specific serum IgE antibodies bound to proteins present in Almond and Brazil nut extracts, indicating that Ara h 2 shares IgE-binding epitopes with Almond and Brazil nut allergens (18). The biological activity of cross-reactive IgE antibodies between Peanut, Brazil nut and Almond has been demonstrated (19).

The Lipid Transfer Proteins are major allergens of *Rosaceae* fruits and will result in varying degrees of cross-reactivity with other family members, as well as between Almond and non-family-related food containing LPT allergens (20-21). For example, Apricot LTP has a sequence identity of 91% and 94% with Peach and Almond LTPs, respectively. (22) Hazel nut LTP has a 62% amino acid homology with the LTP from Almond, 59% with Peach LTP and 59% with Cherry LTP. (5) Apricot LTP has a sequence identity of 91% and 94% with Peach and Almond LTP, respectively (7).

Pru du 4 is a profilin, and cross-reactivity between Almond profilin and other profilin-containing plants is possible (10). Almond and Ryegrass profilin were shown to be mutually inhibitable, so there must be cross-

reactivity with grass pollen profilin (9). As profilin is susceptible to denaturation, variable reactivity will result (10).

The existence of common antigenic bands between Pine nut and Almond has been reported, and this may result in cross-reactivity between these foods (23-24).

In an *in vitro* study, Pru du Amandin has been reported to be cross-reactive with a minor 50 kDa protein of Maize (a gamma-zein), as well as having low cross-reactivity with the 27 kDa gamma-zein. The 50 kDa Maize gamma-zein also reacted with IgE from pooled human sera of patients with self-reported severe Almond allergy (25).

An association between pollen allergy and Almond allergy has been reported. Almost 33% of Birch pollen-allergic patients were reported to also be hypersensitive to Almond and Cherry (26-27). Among 120 patients with pollen allergy and 80 patients with pollen-associated food allergy (as evaluated by skin prick tests, IgE antibody determinations, and HLA genotyping), monovalent pollen allergy was observed in 57% of the pollinosis patients, but in only 15% of patients with food allergy. Hazel nut (71%), Almond (65%), Walnut (44%) and Apple (41%) were the most common food allergens and were frequently associated with allergy to Birch pollen allergy (28).

In a study of 61 patients with a documented history of IgE-mediated reactions to Grape or its products (wine, juice, and wine vinegar), 81.9% were co-sensitised to Apple, 70.5% to Peach, 47.5% to Cherry, 32.8% to Strawberry, 49.2% to Peanut, 42.6% to Walnut, 31.1% to Hazel nut, 26.2% to Almond, and 29.5% to Pistachio. Whether this was due to the presence of panallergens was not elucidated (29).

Clinical Experience

IgE-mediated reactions

Almond may frequently result in sensitisation (30) and may commonly induce symptoms of food allergy (7,11,23,31-36). In general, nut allergies are potentially life-threatening and uncommonly outgrown, and appear to be increasing in prevalence. In studies of patients with nut allergy (adults and children), Peanuts are usually found to be the commonest cause, followed by Brazil nut, Almond, and Hazelnut (37). Other reports have indicated that the most common tree nut allergies are to Walnut, Almond, and Pecan nut. Initial reactions are reported to usually occur at home and in children, at 5 years of age on average. Adverse effects result from a first exposure in 72% of cases. Eighty-nine percent of the reactions involved the skin (urticaria, angioedema), 52% the respiratory tract (wheezing, throat tightness, repetitive coughing, dyspnoea), and 32% the gastrointestinal tract (vomiting, diarrhoea). Two organ systems were affected in 31% of initial reactions, and all 3 in 21% of reactions. Approximately 1/3 of Peanut-allergic individuals will have a co-existing tree nut allergy.

In a retrospective study of 213 Australian children with Peanut or tree nut allergy, 177 patients (83.1%) had Peanut allergy, 27 (12.6%) had Cashew allergy, and 9 had allergy to other tree nuts (4.2%; 2 each to Almond and Pecan, 1 each to Hazel nut and Walnut, and 3 to a mixture of nuts) (38). A cross-sectional, descriptive, questionnaire-based survey conducted in schools in Toulouse, France, found that of 2,716 questionnaires returned, 192 reported a food allergy. Tree nut allergy was self-reported in 19 (7.8%), with 10 for Hazel nut, 6 for Walnut, 2 for Almond and 1 to Cashew. (39) In an American study of 115 patients aged 4-19.5 years, 37% reported an allergy to 1 or more Tree nuts; 19% reported mild adverse reactions to Almond, and 1 patient experienced severe adverse effects (40). An earlier study, by the Food Allergy and Anaphylaxis Network (FAAN) Peanut and Tree Nut Allergy Registry in the USA, collected data on 5,149 patients (mainly children) and reported Walnut as the first cause of allergic reactions to Tree nuts in 34%, followed by Cashew (20%), Almond (15%), Pecan (9%), and Pistachio (7%) (41).

Accidental ingestion occurs frequently outside of the home. As rather low levels of Almond proteins can provoke an allergic reaction in sensitised individuals, these reactions often require emergency treatment

(42). Kiss-induced allergy, a form of allergy by proxy, may occur with Almond, and symptoms may be local or general, mild, moderate or severe. A careful history will determine that the symptoms appeared within minutes after a kiss, the time between eating the allergen and the kiss being quite variable, from a few minutes up to 2 hours (43). Even traces of residual Almond protein in Almond nut oil may pose a threat to patients with allergy, depending on the method of manufacture and processing (44). Anaphylaxis may thus be a common presenting complaint (1,45). An Italian study describes 5 patients with Almond allergy, who were shown to have skin reactivity for Almond. Four patients experienced oral allergy symptoms and anaphylaxis, whereas 1 only experienced oral allergy syndrome, with itching of the oral cavity and rhino-conjunctivitis (1).

A review was done of 601 patients aged 1 to 79 years of age who had experienced anaphylaxis. Of the 133 food reactions, Peanut was responsible in 25, tree nuts in 13, and Almond or Peach in 5 (46).

The sudden and unexpected death of an individual following the ingestion of Hazel nuts and Almonds, to which the individual had not been previously known to be allergic, was described. After eating a dessert containing these nuts, he experienced symptoms of his throat closing and swelling of his lips. He had previously experienced similar symptoms after ingesting Peanuts but had thought nothing of it after being assured that no contact with Peanut was possible. He suddenly collapsed during vigorous dancing. The death was not associated with cutaneous or laryngeal manifestations of anaphylaxis (47).

Other cutaneous symptoms described include acne vulgaris (48) and atopic dermatitis (49). A 5-month-old child with atopic dermatitis developed contact dermatitis to Almond. Persistent eczema correlated with the application of Almond oil on the cheeks and buttocks. The child had not ingested Almond, and her mother did not report Almond intake during her breast-feeding. IgE antobodies to Almond was detectable. Sensitisation appeared to occur from a percutaneous route.

Asthma may occasionally be associated with Almond. In the evaluation of 163 food-allergic asthmatic children for food-induced asthma, using DBPCFC, 1.5% of the group demonstrated Almond as a culprit (25).

Other reactions

Cyanide poisoning after Bitter almond (*Prunus amygdalus var. amara*) ingestion has been reported (50).

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Hordeum vulgare

Family:	*Poaceae* (*Gramineae*)
Common names:	Barley, Barleycorn
Source material:	Untreated planting seeds
See also:	Barley g201, Malt f90, and Gluten f79

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Allergen Exposure

Geographical distribution

This hardy cereal grain is native to Mesopotamia, and its use dates back to the Stone Age. Barley is the fourth most important grain in the world, after Wheat, Maize and Rice. Most of the Barley now grown in the Western world is used either for animal fodder or, when malted, in the brewing and distilling industries. Barley is an erect annual grass, producing grain in bristly-bearded terminal spikes.

Environment

About half of the total US production is used for malting, but because of Barley's mild flavour and soft texture, the grain is often found in soups and baby foods. Malt is used in making several kinds of alcoholic beverages, most prominently beer and whiskey. Other products are flour, flakes and bran. Scotch and Hulled barley are types with only the outer husk removed. Pearl barley is rounded and polished after the husk is removed. Barley flour is ground from Pearl barley and must be combined with a Gluten-containing flour for use in yeast breads. When combined with water and lemon, Pearl barley is used to make Barley water, an old-fashioned restorative for invalids. Barley is a good source of B vitamins and some minerals.

Allergens

A number of allergens have been isolated from Barley. In 132 Pig farm-workers, 43 showed IgE reactivity to 15 components of Barley with molecular masses ranging from 14 kDa to 148 kDa. The major allergen appeared to be a 37 kDa protein and was found in 32 (74.4%) of the 43 immunoblot-positive serum samples. Components of about 55 and 67 kDa reacted with 26 (60.5%) and 18 (41.9%) of the positive serum samples, respectively (1). These proteins may be similar to those in a study reporting that Barley flour proteins of 69, 52 and 10 kDa had been identified in serum from Wheat-hypersensitive individuals and appeared to be major allergens (2).

A number of allergens have been characterised:

Hor v 15, a 16 kDa protein, previously known as Hor v 1, an alpha-amylase/trypsin inhibitor (3-12).

Hor v 16, an alpha-amylase (3,13)

Hor v 17, a beta-amylase (3).

Hor v 21, also known as hordein (3,14-15).

Hor v LTP, a 10 kDa protein, a lipid transfer protein (7,9,14,16).

Hor v Z4, a 45 kDa protein (9,14).

The allergens Hor v 1, Hor v 2, Hor v 4, Hor v 5, Hor v 9 (now known as Hor v 5), Hor v 12 and Hor v 13 have been isolated and characterised from Barley pollen.

Barley seed proteins that could be involved in the foaming properties of beer were investigated. From Barley to Malt and to beer, most of the heat-stable proteins were reported to be disulfide-rich defence proteins, *e.g.*, serpin-like chymotrypsin inhibitors (protein Z), amylase and amylase-protease inhibitors, and lipid transfer proteins (14). The main residual allergens in beer that may result in allergic reactions are the residual lipid transfer protein allergen or Hor v Z4 from Barley (7,9). In individuals who experienced urticaria from beer, analysis of their sera demonstrated that IgE bound only a 10 kDa protein (found also in Malt). In sera of the control patient group, individuals with baker's asthma from Barley flour, a 16 kDa allergen was implicated. Because of the severity of the allergic manifestations to beer, the researchers recommend testing for sensitivity to this beverage those atopic patients who are positive to Malt/Barley and/or who exhibit urticarial reactions after drinking beer (7).

In the case of a 21-year-old atopic woman who developed urticaria, angioedema of the face, a wheeze and dyspnoea shortly after drinking beer and after eating a Maize snack, immunoblotting demonstrated several IgE-binding bands at 31-56 kDa in Malt and Barley extracts, and a major band at 38 kDa in the beer extract (17).

Furthermore, Gluten from Barley can be present in beer, as a result of the addition of Malt. However, a study demonstrated that Gluten levels decreased due to precipitation during the mashing process, during primary and secondary fermentation and, lastly, as a result of adsorption during beer stabilisation. The Gluten content in beer was approximately 3 orders of magnitude lower than in the raw Malt (18).

In baker's asthma, where Barley is implicated, Hor v 15, an alpha-Amylase/Trypsin inhibitor has been shown to be a major allergen (6,8,12).

The major Wheat allergen associated with exercise-induced anaphylaxis is an omega-5 gliadin. Gamma-70 and gamma-35 secalins in Rye and gamma-3 hordein, or Hor v 21, in Barley have been shown to cross-react with omega-5 gliadin, suggesting that Rye and Barley may also elicit symptoms in patients with Wheat-dependent, exercise-induced anaphylaxis (15).

Barley lipid transfer protein (LTP1) is a heat-stable and protease-resistant albumin that concentrates in beer, where it participates in the formation and stability of beer foam. Whereas Barley LTP1 does not display any foaming properties, the corresponding beer protein is surface-active as a result of glycation by Maillard reactions on malting, acylation on mashing, and structural unfolding on brewing (19). Barley LTP (and protein Z(4)) have been identified as the main beer allergens (9).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (20). Cross-reactivity with other species within the *Poaceae* family can be expected, as well as with other species within the genus *Triticum*.

RAST inhibition tests have demonstrated cross-antigenicity among different cereal grains. The degree of cross-reactivity closely paralleled their taxonomic relationship and appeared to be in the following order of decreasing closeness: Wheat, Triticale, Rye, Barley, Oat, Rice and Maize (21). Other studies have demonstrated cross-allergenicity between Rye and Barley, and among Wheat, Rye and Barley. The major allergen was thought to be Gluten, although 16 similar protein bands were detected that were common to all 3 (22-23). Similarly, in patients sensitised to Wheat and Rye flour, IgE antibody investigation indicated that there is significant cross-reaction with seed extracts of Wheat, Durum wheat, Triticale, Rye, Barley, Rye grass, Oats, Canary grass, Rice, Maize, Sorghum and Johnson grass, compared with non-related plants. In particular, significant cross-reactivity was shown among grain extracts of Wheat, Rye, Barley and Oats. Results of this study

suggested that the bran layers of cereal grains are at least as allergenic as the flour (24). The clinical relevance of this is demonstrated in a study of 5 patients with cereal-dependent exercise-induced anaphylaxis and IgE antibodies to Wheat, Rye, Barley and Oats. Wheat gliadin and the corresponding ethanol-soluble proteins of taxonomically closely related cereals were found to be the causative allergens (25). However, in a study examining the IgE specificity of Wheat, Barley and Rye proteins through the use of 2 sera as representative of patients with either Wheat-dependent exercise-induced anaphylaxis (WDEIA) or hypersensitivity to hydrolysed Wheat proteins (HHWP), IgE from a patient with both contact urticaria and food allergy to Gluten hydrolysates cross-reacted with gamma 3-hordein. The pattern of reactivity with Wheat, Barley and Rye proteins differed from that of a WDEIA patient tested under the same conditions (26).

Furthermore, although pollen from these cereals contains unique and specific allergens, the existence of cross-reactivity between Barley and Wheat flour, and between Rye and Wheat flour, as well as among the pollens of cereals and cereal flours, has been suggested (27).

Cross-reactivity among plants containing lipid transfer protein (LTP) is possible but would depend on the specific plants. For example, the lipid transfer protein from Maize was shown to completely cross-react with Rice and Peach lipid transfer proteins but not with Wheat or Barley lipid transfer proteins (17). Rice nonspecific lipid transfer protein closely resembles nonspecific LTPs of Wheat, Barley and Maize, exhibiting a nearly identical pattern of the numerous sequence-specific interactions (28).

A number of Wheat and Barley flour proteins that belong to the cereal alpha-amylase/trypsin inhibitor family have been identified as major allergens associated with baker's asthma. There is complete cross-reactivity among grass, Wheat, Barley, and Rice trypsin inhibitors (13,17,29). However, different allergenic behaviours have been reported to occur among such homologous allergens from Rye, Barley, and Wheat (30).

Cereal alpha- and beta-amylase appear to be important allergens in patients with allergy to flour. RAST inhibition studies have shown minimal cross-reactivity between Barley alpha- or beta-amylase and Barley and fungal alpha-amylase. An association was demonstrated between IgE antibodies to Wheat flour and to Barley alpha-amylase and Barley beta-amylase, but a poor association with fungal alpha-amylase (31).

Gamma-70 and gamma-35 secalins in Rye, and gamma-3 hordein (probably representing Hor v 21) in Barley, have been shown to cross-react with omega-5 gliadin, a major allergen in Wheat-dependent, exercise-induced anaphylaxis (WDEIA). These findings suggest that Rye and Barley may also elicit symptoms in patients with Wheat-dependent, exercise-induced anaphylaxis (15). Due to this cross-reactivity, treatment with a Gluten-free diet, *i.e.*, a diet excluding Wheat, Rye, and Barley, is indicated for all patients with WDEIA (32).

Prolamines extracted from Wheat (gliadin), Rye (secalin), Barley (hordein) and Oats (avenin) were used to raise antibodies in rabbits. The close botanical relationship between Wheat and Rye, and, to a lesser extent, between these and Barley, is clearly established. The cross-reactivity of gliadin, secalin and hordein with anti-avenin serum was found to be weak. In contrast, avenin shows a strong cross-reactivity with anti-gliadin serum (33).

A degree of homology among amylase/protease inhibitors, acyl-CoA oxidase and fructose-bisphosphate-aldolase from Wheat, Barley, Maize, and Rice has been reported but requires further elucidation (34).

Clinical Experience

IgE-mediated reactions

Barley may commonly induce symptoms of food allergy in sensitised individuals. (1) Symptoms may include gastrointestinal distress, atopic dermatitis and urticaria, angioedema, anaphylaxis and food-dependant, exercise-induced anaphylaxis, wheezing and baker's asthma. Cough, wheezing, shortness of breath, fever, stuffy

nose, and skin itching/rash on exposure to grain dust have also been reported, as well as "grain fever" (35).

In a study of cereal allergy and atopic dermatitis, on oral provocation, 18 children exhibited a positive response to Wheat, 3 to Rye, 1 to Barley, and 1 to Oats. Symptoms were dermatologic, gastrointestinal, or oropharyngeal, and their onset after provocation was immediate in 8, delayed in 14, and both immediate and delayed in 1. A combination of SPT, IgE antibody determination and histamine-release tests detected all those with immediate reactions and 9/14 with delayed reactions. Of 5 subjects negative to these tests, 3 were positive on patch or lymphocyte proliferation tests (36).

In a study evaluating the allergic reactivity to ingested and inhaled cereal allergens at different ages among 66 patients, 40 children aged 3 to 6 months experienced diarrhoea, vomiting, eczema or weight loss after the introduction of cereal formula into their diet. Coeliac disease was excluded in all. The most important allergen was Wheat, followed by Barley and Rye. Among adults with cereal allergy, sensitisation to other allergens was common, especially to Lolium perenne (Rye grass) pollen (37).

Anaphylaxis following the ingestion of Barley may occur. These reactions may be to residual Barley proteins in beer. In 2 cases of severe systemic reactions due to beer ingestion, 1 required emergency care, and the other presented with generalised urticaria and angioedema (38). A 21-year-old woman is described who developed urticaria, angioedema of the face, a wheeze and dyspnoea shortly after drinking beer and after eating a Maize snack. She was shown on immunoblotting studies of her serum to have antibodies to allergens in Malt and Barley extracts present in the beer. The authors concluded that the patient had developed type I hypersensitivity to Barley, Malt and Maize (18).

Food-dependent exercise-induced anaphylaxis may result from ingestion of Barley (15,39). In 5 patients with cereal-dependent exercise-induced anaphylaxis and IgE antibodies to Wheat, Rye, Barley and Oats, Wheat gliadin and the corresponding ethanol-soluble proteins of taxonomically closely related cereals were found to be the causative allergens (26). Thus, Rye and Barley may elicit these symptoms in patients with Wheat-dependent, exercise-induced anaphylaxis, and *vice versa* (15). Due to this cross-reactivity, treatment with a Gluten-free diet, *i.e.*, a diet excluding Wheat, Rye, and Barley, is indicated for all patients with WDEIA. In an evaluation of sera of 2 patients with either Wheat-dependent exercise-induced anaphylaxis (WDEIA) or hyper-sensitivity to hydrolysed wheat proteins, in the latter patient, who experienced both contact urticaria and food allergy to Gluten hydrolysates, IgE was shown to also cross-react with gamma 3-hordein (Hor v 21) (27).

Barley may also result in occupational allergy in bakery and other food industry workers, liqueur and spirit manufacturers, and farmers. Barley may commonly result in baker's asthma (28). Barley alpha-amylase/trypsin inhibitors have been identified as major allergens associated with baker's asthma (30). Asthma related to exposure to cereal flour contained in animal formula feeds has been reported (40). Similarly, flour made from Barley resulted in IgE-mediated occupational respiratory symptoms in Pig farm workers in southern Taiwan (1).

Occupational asthma paired with asthma following oral ingestion of Barley flour and beer made from Barley has also been reported. A 50-year-old man developed asthma both after exposure to feeding stuffs and flours and after ingestion of beverages made of cereal flour. Allergy to Barley flour (and Maize flour and mites) was demonstrated by skin reactivity and allergen-specific IgE. A bronchial challenge test with Barley flour resulted in an immediate positive response (41).

Cereal flours are used in the wood industry to improve the quality of the glues necessary to produce veneer panels in wood manufacturing. Three workers were found to be allergic to cereal alpha-amylase inhibitors, proteins cross-reactive proteins found in Rye, Barley and Wheat (4).

Occupational asthma may also occur to Barley grain dust. A report was made of a 32-year-old storeman who dealt with the packaging of Wheat flour, Barley and Peanuts. He developed immediate symptoms of sneezing, cough and dyspnoea on exposure to Barley (42).

Alpha-amylase allergens have been identified as a major allergen in baker's asthma (12).

Other reactions

Barley may result in or exacerbate atopic dermatitis (24) or contact dermatitis (43).

Barley may also cause coeliac disease, an autoimmune disease resulting in a food-induced enteropathy, which occurs following exposure to prolamins (Gluten) in Wheat, Rye, and Barley (44-45).

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe, cell-mediated gastrointestinal food hypersensitivity typically provoked by Cow's milk or Soy but sometimes by other foods, including Barley. Symptoms of typical FPIES are delayed (median: 2 hours) and include vomiting, diarrhoea, lethargy and dehydration. Initial presentation is severe in 79% of patients, prompting evaluation for sepsis and hospitalisation for dehydration or shock. FPIES appears not to occur to maternally ingested foods through breastfeeding, but does occur if the offending food is fed directly to the infant (46).

The ingestion, by a largely illiterate population in Iraq, of Wheat and Barley seed treated with an alkyl mercury fungicide for sowing led to a major outbreak of poisoning with a high fatality rate (47).

Six cases of acute exogenous allergic alveolitis after loading mouldy Barley have been reported (48).

Malt, a product of Barley, may result in immediate-type reactions. (See Malt f90.) Malt extract is made from germinating Barley. In a patient allergic to Malt, the allergic reactions usually occurred after consumption of Malt-containing chocolate drinks and Malt-containing snack products (18,49).

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f310 Blue vetch

Lathyrus sativus

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Blue vetch, Grasspea, Chickling pea, Chickling vetch
Source material:	Dried seeds

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Allergen Exposure

Geographical distribution

Blue vetch is found in Eurasia, North America, temperate South America and East Africa. But the geographical origin of *Lathyrus sativus* is unknown.

Blue vetch is a many-branched straggling or climbing herbaceous winter annual with stems up to 90 cm tall. It produces a drought-resistant, high-yielding, nitrogen-rich pulse with high-quality protein and carbohydrate. The seeds are used for food (which may be an exclusive food during times of drought or famine) and livestock feed, and the plant as green manure and a cold-weather forage crop, and for erosion control.

Environment

Lathyrus sativus is a high-yielding, drought-resistant legume consumed as a food in northern India and neighbouring countries, as well as in Ethiopia. Its development into an important food legume, however, has been hindered by the presence of the neurotoxin beta-N-oxalyl-L-alpha,beta-diaminopropionic acid (beta-ODAP), which, if consumed in large quantities for prolonged periods, can cause irreversible paralysis (1). The flour is used in cattle feeding and industrial processing in some countries (2).

The plant is found in cultivated beds or as a relict of cultivation; no truly wild stands exist. The immature seed can be eaten like Green peas. The mature seed is eaten roasted or boiled, after soaking or parching, and the young shoots can also be cooked. The seed is often used in making dhal, paste balls for curry, or beverages. It can also be ground into a powder and mixed with Wheat to make protein-enhanced bread. The seeds are used locally in homeopathic medicine.

Unexpected exposure

See under Environment. Blue vetch as a dried legume is used in some regions of Spain in the form of flour for cooking and has been responsible for some cases of allergic reactions through food intake or contact (3).

Allergens

No allergens from this plant have yet been characterised.

More than 60% of the seed comprises globulin proteins, and 30% albumins. A single 24 kDa polypeptide comprises more than half of the protein present in the albumin fraction. The globulins may be fractionated into 3 main components, which are named alpha-lathyrin (the major globulin), beta-lathyrin, and gamma-lathyrin (4).

Blue vetch flour shows a complex allergenicity. Most allergens are said to be thermostable (3), but researchers in other studies suggest that some or all allergens in Blue vetch may be heat-labile, resulting in Blue vetch-allergic individuals being able to ingest cooked Blue vetch products (13).

In a study of sera from 38 Spanish legume-sensitised patients, 77% were shown to have skin reactivity to Blue vetch flour; 4 of whom had developed clinical symptoms to Blue vetch, and 2 of whom, in addition, to other legumes. No protein bands were identified by IgE antibodies to extracts boiled for 15 minutes, whereas 20 protein bands were identified to raw Blue vetch extracts. Serum IgE bound most frequently to protein bands of 50.9 and 27.7 kDa. Only 2 allergens of molecular weights 27.7 and 12.9 kDa were identified by sera from the subjects who were sensitive only to Blue vetch (3). Other studies have indicated the presence of allergens of 46, 32 and 28 kDa (2).

A 24 kDa protein was purified from the seeds of *Lathyrus sativus*. The N-terminal amino-acid sequence showed significant homology with the 2S albumin class of seed storage proteins. The protein showed 85% sequence homology with the seed albumin of *Pisum sativum* (5). However, its allergenicity was not evaluated.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact is not seen frequently (6). In an *in vitro* study, the specific IgE binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked among the extracts of Peanut, Garden pea, Chick pea, and Soybean (7-8). However, clinical studies have found that there is little cross-reactivity among members of the *Fabaceae* (*Leguminosae*) (9-11).

Cross-reactivity and/or co-sensitivity have been reported among Blue vetch, Chick pea, and Lentil (12).

Clinical Experience

IgE-mediated reactions

Blue vetch may uncommonly induce symptoms of food allergy and occupational allergy in sensitised individuals.

Sera from 38 Spanish legume-sensitised patients were used to assess the allergenic composition of Blue vetch. Seventy-seven percent of patients showed a positive skin test to Blue vetch flour; 4 of these patients had developed clinical symptoms in relation to Blue vetch, and 2 of them, in addition, to other legumes (3).

A study reports on a 10-year-old child with asthmatic attacks related to *Lathyrus sativus* flour inhalation. This child had a history of perennial rhinitis, and bronchial asthma was reported. In the previous year, shortly after exposure to Blue vetch flour in the family store, he had experienced sneezing, rhinorrhoea, wheezing and dyspnoea attacks. Avoiding exposure resulted in a marked reduction of symptoms, and he became asymptomatic. He tolerated the ingestion of foodstuffs prepared from this legume, as well as exposure to other types of flours. Skin test with the raw extract was positive, and negative for the heated extract. Specific bronchial provocation challenge was markedly and immediately positive. IgE antibodies to *Lathyrus sativus* flour were demonstrated by indirect enzyme immunoassay. The authors suggest that the loss of allergenic sensitivity observed in the cutaneous test with heated Blue vetch may indicate the reason this patient was able to ingest cooked foodstuffs prepared with this flour without reacting (13).

Two young women experienced symptoms after eating Blue vetch. They reported previous hypersensitivity to other legumes (14).

Generalised urticaria and facial oedema in a 5-year-old, occurring a few minutes after ingestion, have been reported (15).

f310 Blue vetch

Occupational asthma has been reported following exposure to flour made from Blue vetch. This flour is used in the industrial processing of parquet (wood flooring). A 55 years old man is described, who reported a one year long history of rhinorrhoea, paroxysmal sneezing, eyes and nasal pruritus, and wheezing dyspnea with coughing and chest tightness, symptoms which were related to his working with Blue vetch flour. Symptoms abated during holidays and weekends. He had worked in direct contact with Blue vetch flour for 15 years, which involved the production of a sealant for wooden floor panels. He had never eaten Blue vetch and did not experience adverse effects ingesting other legumes. Skin prick test with the extract showed a positive immediate response. IgE antibody level to grass pea was 9.57 kU_A/l. Specific bronchial challenge test elicited an immediate response, both clinically (rhinitis, cough, dyspnoea, chest tightness) and with a 20% decrease in FEV_1 at 5 minutes (2).

A 42-year-old man was described who had worked as a carpenter for 6 years and who reported a history of rhinorrhoea, paroxysmal sneezing, nasocular pruritus, lacrimation, wheezing and dyspnoea attacks while preparing a mixture to seal the junctures between wooden panels. Skin prick tests with Blue vetch and Lentil extracts were positive. IgE antibody level to Blue vetch was 0.62 kU_A/l. Histamine release tests were positive. Bronchial challenge with Blue vetch was positive within 5 minutes, with a decrease in FEV_1 of 20%. He also developed rhinoconjunctivis. The authors point out that in cases of occupational asthma to Blue vetch flour, patients tolerate the cooked food (16). As suggest by other authors as well, some or all allergens in Blue vetch are heat-labile, resulting in Blue vetch-allergic individuals being able to ingest cooked Blue vetch products (13).

Occupational asthma to a close relative, Sweet pea (*Lathyrus odoratus*), has also been described (17).

Other reactions

Neurolathyrism is a neurological condition seen among people who eat the seeds of *Lathyrus sativus* as a principal source of food energy for 2 months or more. It is characterised by severe muscular rigidity and irreversible spastic paralysis of the lower limbs, spinal hyperreflexia, and structural changes of the skeleton and connective tissue (18-19). Once prevalent throughout Europe, N. Africa, the Middle East and parts of the Far East, the disease is presently restricted to India, Bangladesh and Ethiopia (20). The biochemical mechanism involves beta-N-Oxalyl amino-L-alanine (L-BOAA); a synonym is beta-N-oxalyl-alpha,beta-diaminopropionic acid (beta-ODAP). This is a naturally occurring non-protein amino acid present in Blue vetch. Ingestion of L-BOAA in a staple diet results in a progressive neurodegenerative condition, a form of motor neuron disease that affects the upper motor neurons and anterior horn cells of the lumbar spinal cord. L-BOAA is an excitatory acid and acts as an agonist at the AMPA receptor (21-22).

The oil from the seeds is a powerful and dangerous cathartic that contains a poisonous principle, probably an acid salt of phytic acid.

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f18 Brazil nut

Bertholletia excelsa

Family: *Lecythidaceae*

Common names: Brazil nut, Para-nut, Cream nut

Source material: Shelled nuts

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Allergen Exposure

Geographical distribution

The Brazil nut is actually the seed of a giant tree that grows wild in South America's Amazon jungle. The seeds, about 6 cm long, come in clusters of 8 to 25 inside a large, hard, thick-walled globular pod that resembles a Coconut and weighs up to 2 kg. The extremely hard shell of each seed is dark-brown and 3-sided. The kernel is white and high in oil, containing about 70% oil and 17% protein. When fresh it is highly esteemed for its rich flavour, but it becomes rancid in a short time from the great quantity of oil it contains. Except for its close relative the Paradise nut, it is not closely related to any other food.

Brazil nut exportation from the Amazon was begun in the 1600s by Dutch and Portuguese traders. The monetary value of the nuts (nearly all from wild trees) is second only to that of rubber.

Environment

In the Amazon, indigenous tribes eat the nuts raw, or grate them and mix them into gruels, often along with Manioc flour. The plentiful oil is used in cooking. Exported, the nuts are a snack food, and their oil is prized. In addition to protein and fat, Brazil nuts are a substantial source of selenium, an important antioxidant. The proteins, though making up only 15-17% of the nuts' fresh weight, comprise 50% of the defatted flour. Storage proteins are the most important ones, and the 12S globulin legumin-like protein and the 2S albumin have been identified as the most representative. The 2S protein is high in sulfur-rich amino acid (3-8% cysteine and 18% methionine) (1). The proteins are also extremely rich in glutamine, glutamic acid, and arginine.

The tree bark is brewed into tea to treat liver ailments. The husks of the seed pods have also been brewed to treat stomach aches.

Unexpected exposure

Brazil nut may be a “hidden” allergen in cookies, etc. The oil extracted from the nuts is commonly used in Peru and other South American countries to manufacture soap, and for lighting, and the empty pods are used as implements and burned to repel insects. Worldwide, Brazil nut oil is often used in soaps, shampoos, hair conditioning/repair products, and skin moisturisers, and extracts of the pods can figure in insect repellents.

Allergens

A number of allergenic proteins has been isolated from Brazil nut. These range in size from 4 kDa to 58 kDa. In a study of a group of patients with IgE antibodies to Brazil nut, comprising 11 patients with anaphylaxis to eating Brazil nuts and 10 asymptomatic subjects, sera from all the symptomatic patients recognised a 9 kDa allergen corresponding to 2S albumin of Brazil nut, whereas the other allergens each bound IgE antibodies from less than 50% of sera. No

IgE binding to the 9 kDa allergen occurred in sera from asymptomatic subjects, but allergenic proteins of 25 to 58 kDa were recognised and were identified as minor allergens (5). Other minor allergens have been detected: of 18, 25, 33, and 45 kDa (2), including a 12S globulin protein, which is a legumin-like storage globulin (1).

The allergens characterised to date are:

Ber e 1, a 9 kDa protein, a 2S albumin, resistant to digestion by pepsin, and a major allergen (3-14).

Ber e 2, an 11S globulin-like protein (10,13,15).

The main immunoglobulin E epitope region of the 2S albumin, Ber e 1, is very stable to gastric digestion (3,8,16).

The Brazil nut 2S albumin has been recognised as a methionine-rich protein that could be used to increase the nutritional value of certain foods through genetic engineering techniques. However, the 2S albumin of the Brazil nut is also the major allergen of Brazil nuts (Ber e 1) and shows IgE-reactivity with more than 80% of the sera from Brazil nut-allergic subjects. This was demonstrated in transgenic Soybean: the newly expressed protein retained its allergenicity (17-18).

Potential cross-reactivity

An extensive cross-reactivity within the family can be expected (19).

Brazil nut contains a 2S albumin storage protein, a protein common to many seeds, which displays similarity to the 2S albumin of Cotton, Cocoa bean, Sunflower seed, Rape seed, Castor bean, English walnut (Jug r 1), Mustard seed (Sin a 1) and Sesame seed (Ses i 2). Comparison of the amino acid sequence shows high sequence similarity, from 34% between Sunflower seed and Brazil nut, to >52% similarity and >38% identity between Brazil nut and many other plant 2S albumins (20-24). The English walnut allergen (Jug r 1) exhibits a 46.1% identity with the Brazil nut 2S albumin seed storage protein, Ber e 1 (24-25).

The 2S albumins have been shown to play a significant role in cross-reactivity between Walnut Jug r 1 and Pecan nut Car i 1, as a result of the high degree of structural homology of the 2S albumins in these 2 tree nuts. However, a study of the conformational analysis of the linear IgE-binding epitopes mapped on the molecular surface of Ara h 2, a 2S albumin, showed no structural homology with the corresponding region of Brazil nut Ber e 1; this indicates that allergenic cross-reactivity observed between Peanut and Brazil nut may depend on other ubiquitous seed storage protein allergens, *e.g.*, the vicilins (26).

However, a recent study evaluating cloned Peanut Ara h 2 reported that when serum from Peanut-allergic patients is pre-incubated with increasing concentrations of Almond or Brazil nut extract, IgE binding to rAra h 2 is inhibited. Purified rAra h 2-specific serum IgE antibodies also bound to proteins present in Almond and Brazil nut extracts through immunoblotting, which indicates that the Peanut allergen Ara h 2 shares IgE-binding epitopes with both Almond and Brazil nut allergens (27). The same authors had previously reported that Peanut-specific antibodies from sera of Peanut-allergic subjects became activated following stimulation with Peanut, Almond and Brazil nut extracts, demonstrating biological activity of cross-reactive IgE antibodies (28).

A 2S albumin has been isolated from the seed of Tomato and was found to cross-react with antiserum to the fruit lectin. The sequence of the fruit lectin was shown to be similar to that of 2S albumins from different plants, such as Brazil nut and Castor beans (29). The allergenicity of the Tomato seed 2S albumin was not evaluated.

Walnut-induced anaphylaxis has been reported, with cross-reactivity to Hazel nut and Brazil nut described (30).

f18 Brazil nut

Clinical Experience

IgE-mediated reactions

Allergy to Brazil nut is common, frequently has an onset in the first few years of life, generally persists, and accounts for severe and potentially fatal allergic reactions. The ubiquity of this food in the modern diet makes avoidance difficult, and accidental ingestions, with reactions, are common (1,31-36). Symptoms include vomiting, diarrhoea and other manifestations associated with food allergy: laryngeal oedema, atopic dermatitis, urticaria and anaphylaxis (1, 36-37).

The probability of patients with nut allergy having IgE antibodies to a particular combination of Peanut, Hazel nut and Brazil nut is similar, whatever the patients' age or sex. The apparent increase in multiple nut reactivity with increasing age may therefore be due to exposure of previously unchallenged sensitivity. The frequency of multiple-nut specificity is sufficiently high that patients should always be tested for allergy to a range of nuts if they have a history of reacting to any nut (38). In a study of 62 patients (adults and children) with nut allergy, Peanuts were the commonest cause of allergy (n=47), followed by Brazil nut (n=18), Almond (n=14), and Hazel nut (n=13) (35).

In an American study of 115 patients aged 4-19.5 years, 2% (n=1) were graded as mildly allergic to Brazil nut, and 4% (n=2) were graded as severely allergic. The study also concluded that around 9% of children with tree nut allergy outgrow their allergy. (39) An earlier American study by the Food Allergy and Anaphylaxis Network (FAAN) Peanut and Tree Nut Allergy Registry collected information on 5,149 patients (mainly children) and found that 34% were allergic to Walnut, followed by Cashew (20%), Almond (15%), Pecan (9%), and Pistachio (7%). Less than 5% each were allergic to Hazel, Brazil, Pine, Macadamia and Hickory nuts (40). It is evident that the frequency of reported allergy depends on the population group being studied and that in countries where the consumption of Brazil nut is low, the prevalence of reported allergy to this nut will be low.

A study reports on 11 patients with anaphylaxis after eating Brazil nuts and on 10 subjects with no symptoms to this food, although both groups had IgE antibodies to Brazil nut. A number of allergenic components with molecular weights ranging from 4 to 58 kDa were isolated. All sera from symptomatic patients recognised the Brazil nut 2S albumin, whereas the other allergens each bound IgE antibodies from less than 50% of sera. No sera from asymptomatic subjects showed IgE antibody binding to the 2S albumin, but sera did recognise 25 to 58 kDa components, which are minor allergens (5). Therefore, minor Brazil nut allergens were thought to result only in sensitisation to Brazil nut and not in allergic symptoms (5). However, this is contradicted by a study of a 15-year-old boy who experienced 2 distinct episodes of generalised urticaria about 30 minutes after eating Brazil nut. An IgE antibody test was very positive to Brazil nut. Serum IgE was positive to Brazil nut but negative to Mustard, Poppy seed, Sesame seed and Sunflower seed, suggesting no sensitisation to the 2S albumin allergen (2). The 2S albumins may be very important in food-induced anaphylaxis (6).

Anaphylaxis to Brazil nut has been reported. A British report from the Isle of Wight (population 125,000) described 12 cases of allergy to Brazil nut recorded over 8 years from 1983 to 1991. Eleven patients developed angioedema, 7 generalised urticaria, 5 bronchospasm, 2 stridor, 2 throat tightness, 2 itchy mouth and 1 syncope. Onset of symptoms was less than 1-3 minutes in all. Eight patients were shown to have significant skin reactivity for Brazil nut. In 6 out of 8 patients, Brazil nut IgE antobodies were demonstrated (> 0.7 kU_A/l). In 3 patients there was no definite evidence of IgE-mediated hypersensitivity. Total IgE was normal in 5 patients with severe reactions. Ten out of 12 patients had other atopic diseases such as asthma, eczema or allergic rhinitis, usually from infancy or early childhood. Seven out of 8 patients were positive to several food and/or inhalant allergens on skin test (36).

Anaphylaxis to Brazil nut may occur even with no previous history of ingestion of this nut. This was reported from SPT investigation for Brazil nut sensitisation in a young adult who had experienced an adverse reaction presumed to be a result of allergy to Walnut. Immediately after the skin was pricked with fresh Brazil nut, an episode of severe anaphylaxis occurred, requiring epinephrine and intravenous steroids. The authors thought this might have resulted from cross-reactivity, as occurs with other tree nuts (41).

Anaphylaxis was also reported in a 31-year-old woman, known to have rhinoconjunctivitis and asthma, who developed pharyngeal itching, lip swelling, dysphonia, dyspnoea, wheezing, and generalised macular exanthema 10 minutes after eating a Brazil nut. She had previously developed oral allergy syndrome after eating Almond, Walnut, Sunflower seed, and Hazel nut. She had suffered from abdominal pain after eating Chestnut. She tolerated Peanut and Pistachio. Skin reactivity was detected for Brazil nut, Almond, Peanut, Chestnut, Sunflower seed, Pistachio, Hazel nut, Walnut, and Cashew nut. Serum IgE was raised for Almond, Peanut, Chestnut, Pistachio, Hazel nut and Sunflower seed. IgE antibody level to Brazil nut was 2.37 kU_A/l (37).

Patients sensitised to minor Brazil nut allergens are reported to not have allergic symptoms (5), but this is contradicted by a report on a 15-year-old boy who experienced 2 distinct episodes of generalised urticaria about 30 minutes after eating Brazil nut. SPT and serum IgE was present for Brazil nut. As serum IgE was present for Brazil nut but not for Mustard, Poppy seed, Sesame seed or Sunflower seed, the authors concluded that no reactivity was therefore shown to 2S albumins, which suggests that a minor allergen was involved (2).

Food allergens have been reported to be present in breast milk. A study also reports on a 20-year-old woman with documented Brazil nut allergy who developed widespread urticaria and mild dyspnoea after intercourse with her boyfriend, who had earlier consumed Brazil nuts. SPT evaluation with the boyfriend's semen after Brazil nut consumption confirmed significant reactivity, whereas a sample before nut consumption was negative (42).

In a study to find the best approach to the diagnosis of Brazil nut allergy, 56 children and adults with a history of an allergic reaction to Brazil nut or other evidence of sensitisation were evaluated by questionnaire, SPT and serum IgE antibodies to Brazil nut, and by double-blind, placebo-controlled labial and, if necessary, oral challenges. The study concluded that a combination of history, SPT and IgE antibodies was adequate for achieving a diagnosis in the approximately 77% of patients with suspected Brazil nut allergy. However, a doubtful history combined with SPT result (between 1 and 5 mm), or a IgE antibody level less than 3.5 kU_A/l, may require an oral challenge to help determine the risk of a Brazil nut allergic reaction (43).

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f11 Buckwheat

Fagopyrum esculentum

Family:	*Polygonaceae*
Common names:	Buckwheat, Beechwheat, Fagopyrum, French wheat, Garden buckwheat
Source material:	Whole seeds

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Allergen Exposure

Geographical distribution

Buckwheat is grown almost worldwide, but is especially common in China and Iraq. Its original habitat is obscure. It is a member of the *Polygonaceae* group of weeds. In China another type of Buckwheat, Tartary buckwheat (*Fagopyrum tartaricum*) is grown and consumed (1). Buckwheat is consumed mainly in Asian countries, in particular in Japan, where it is a major food allergen due to the popularity of soba (Buckwheat noodles).

Buckwheat is a large-leafed, herbaceous species and not a grass, and thus not a true cereal. The only other common food plant in this family is Rhubarb. Buckwheat is useful as a substitute for Wheat and other small grains (Rice, Barley, Oats, Rye), in particular as an alternative for people allergic to Wheat.

Environment

Buckwheat grows in cultivated beds and, where it has escaped from cultivation, on waste ground. Buckwheat flour is used for bread and other baked products. The seed is processed to make noodles (termed "soba" in Japan) and is used in soups, cakes, biscuits, etc. The grain can produce edible sprouts and excellent beer. The leaves can be eaten raw or cooked like Spinach. Buckwheat is high in fibre, minerals, vitamins and essential amino acids, especially lysine. It also contains rutin, which is believed to improve cardiovascular health by dilating the blood vessels, reducing capillary permeability, and lowering blood pressure.

Buckwheat is used internally in the treatment of high blood pressure, gout, varicose veins, chilblains, radiation damage, etc. It is best used in conjunction with vitamin C, since this aids absorption. Often combined with Lime flowers (*Tilia* species), it is a specific treatment for haemorrhage into the retina. A poultice made from the seeds has been used for restoring the flow of milk in nursing mothers. An infusion of the herb has been a treatment of erysipelas (an acute infectious skin disease). A homeopathic remedy has been made from the leaves and used in the treatment of eczema and liver disorders.

Unexpected exposure

The hulls of Buckwheat are used as cushion fillings in some Asian countries. A blue dye is obtained from the stems, while a brown dye is obtained from the flowers.

Allergens

Buckwheat is a very potent allergen, causing both food and inhalant allergy. Approximately 30% of total Buckwheat proteins are 2S albumins. These polypeptides range from 8 to 16 kDa, and are water-soluble. (2) However, the allergenicity of these proteins was not evaluated. Using sera from

9 Buckwheat-allergic subjects, major IgE-reactive bands of 73, 70, 62, 58 and 54 kDa were isolated under non-reducing conditions. Under reducing conditions, the 73, 70, 62 and 58 kDa bands split to 56 and 24, 52 and 24, 45 and 24, and 43 and 24 kDa molecules, respectively. The 24 kDa molecule was the most prominent band recognised with IgE as well as IgG and IgA (3).

In a study of 19 Buckwheat-allergic subjects with symptoms after Buckwheat ingestion, and 15 asymptomatic control subjects with positive SPT to Buckwheat, the prevalence of IgE binding to 24 kDa (Fag e 1), 16kDa (Fag e 16kD), and 9 kDa (presumably now recognised as Fag e TI) allergens was assessed. IgE antibodies to split 19 kDa allergens was more often found in Buckwheat-allergic patients than in asymptomatic subjects (78% *vs*. 7%). The amino acid sequence of the 19 kDa and 16 kDa allergens showed moderate and weak homology to the 19 kDa globulin protein of Rice and the alpha-amylase/trypsin inhibitor of Millet, respectively. The 9 kDa isoallergens were similar to each other and were identified as trypsin inhibitors. The authors concluded that the allergens of 24, 19, 16, and 9 kDa were strong major allergen candidates for Buckwheat, and that the 19 kDa allergen was relatively specific for Buckwheat-allergic patients (4). Studies by other researchers have suggested that 14 and 18 kDa Buckwheat allergens are major allergens (5), and an earlier study reported the isolation of 22 kDa, 36 kDa, 39 - 40 kDa and 70 - 72 kDa allergens that were identified from water-soluble fractions of Buckwheat (6).

An 8S storage globulin from Buckwheat, with the structure common to the vicilin-like family of seed storage proteins, was isolated; its increase precedes that of the 13S globulin (the main Buckwheat storage protein) and starts from an early stage of Buckwheat seed development, continuing to accumulate throughout seed development to contribute approximately 7% of total seed proteins. A 13S Buckwheat legumin of 23-25 kDa, reported to be a major Buckwheat allergen, was also isolated. A partial cDNA showed high homology with cDNAs coding for vicilin-like storage proteins from various plant species (7).

The following allergens have been characterised:

Fag e 1, previously known as BW24KD, a 22 - 24 kDa protein, an 11S Globulin-like legumin (3,6,8-11).

Fag e 10kD, a 8-17 kDa protein, a 2S albumin (12-13).

Fag e 16kD, a 16 kDa protein, a 2S Albumin. (9,12,14-15).

Fag e 19kD, a 19 kDa vicilin-like protein. (9,15).

Fag e TI, a trypsin inhibitor (4,16-17).

Studies have elaborated on the characterised allergens, and a number of other proteins have been isolated but not characterised.

Fag e 10kD is also a major allergen of Buckwheat and was reported to sensitise approximately 57% of Buckwheat-allergic patients (13). Interestingly, not all species of Buckwheat contain the major allergen found in *F. esculentum*. *F. lineare* and *F. urophyllum* have been shown to lack the 22 kDa major allergenic protein (18).

The 16 kDa protein of Buckwheat, also a major allergen, has 50% homology to the reported 8 kDa Buckwheat allergen which is a 2 S storage albumin. Using a re-combinant 16 kDa allergen, it was found that approximately 77.8% of 18 patients with Buckwheat allergy had raised IgE antibody level to this allergen, compared to none of 20 asymptomatic Buckwheat-sensitised subjects (14).

In an assessment of the 19 kDa allergen, about 83.3% of Buckwheat-allergic patients were shown to have IgE antibodies raised to the recombinant 19 kDa protein, compared to only 1 of the 19 asymptomatic Buckwheat-sensitised subjects, suggesting that the 19 kDa Buckwheat allergen may be a major allergen (15).

Allergens of 14 and 18 kDa have been isolated and shown to share some homology with Rice proteins. Both are major allergens (5). Another major allergen, a 24 kDa protein, bound to IgE antibodies in sera from every Buckwheat-allergic patient in a study (1,19).

f11 Buckwheat

A16 kDa Buckwheat protein that was isolated has been shown to be resistant to pepsin digestion and was reported to be responsible for immediate hypersensitivity reactions, including anaphylaxis. Allergen-specific IgE was detected to a pepsin-sensitive 24 kDa protein but was not thought to play a role in immediate hypersensitivity reactions. However, the 24 kDa protein, previously reported to be a major allergen and now recognised as Fag e 1, reacted to IgE antibodies present in sera from almost all subjects (19/20) regardless of symptoms. On the other hand, 16 and 19 kDa proteins bound with IgE antibodies present in sera from 9 of the 10 patients with immediate hypersensitivity reactions, including 8 patients with anaphylaxis; but not with sera from Buckwheat-specific IgE-positive subjects without immediate hypersensitivity reactions. After pepsin treatment, the 16 kDa protein but not the 19 and 24 kDa proteins remained undigested and preserved the capacity of IgE binding (9).

In an analysis of Buckwheat-specific IgE antibodies in an 8-year-old with fatal food-dependent exercise-induced anaphylaxis, 7 protein bands were found that reacted with the IgE of the patient's serum. Four bands of 16, 20, 24, and 58 kDa were specific to the patient, compared to subjects not allergic to Buckwheat (20).

Buckwheat seed contains a thiamin-binding protein. The protein has homology with the thiamin-binding proteins from Rice seeds and Sesame seeds (21). A 230 kDa thiamin-binding protein has been isolated from Sunflower seeds; its properties are similar to those in proteins from Buckwheat seeds, but not to those from Rice seeds and Sesame seeds; and similar to those of helianthinin (22). The clinical significance of this protein has not been established. Similarly, the significance of the inhibitor of trypsin and chymotrypsin is unknown (23).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (24). Importantly, Buckwheat is not taxonomically closely related to Wheat or other cereal grains. The 24 kDa allergenic protein in Tartary buckwheat shares a greater than 93% homology with the allergenic storage protein and a legumin-like protein from Common buckwheat (25).

Immediate hypersensitivity reactions induced by the ingestion of Buckwheat are considered to be IgE-mediated. In 28 subjects without immediate hypersensitivity reactions to Buckwheat ingestion, out of 46 subjects in whom IgE antibodies to both Buckwheat and Rice allergens were detected, results led to the conclusion that there is cross-reactivity with IgE antibodies between Buckwheat and Rice and that IgE antibodies from subjects without immediate hypersensitivity reactions might recognise the epitopes on Buckwheat antigens which cross-react with Rice antigens, whereas IgE antibodies from subjects with immediate hypersensitivity reactions might bind to Buckwheat-specific epitopes (26-27).

Cross-reactivity between Buckwheat and Natural rubber latex has been reported; therefore, allergy to fruits and vegetables that cross-react with Latex should be considered in patients who are proven to be allergic to Buckwheat (28-29). Immunochemical cross-reactivity between the globulins from Buckwheat and Indigo seeds has been documented (30).

The 19 kDa Buckwheat allergen has a weak homology to the vicilin-like allergens of Cashew (Ana o 1), English walnut (Jug r 2) and 7 S globulin from *Sesamum indicum*. (15) Cross-sensitisation of Poppy seed with Buckwheat has been reported (31).

Clinical Experience

IgE-mediated reactions

Buckwheat has been recognised as a common food allergen in Korea, Japan, and other Asian countries, but not in Taiwan (32-33). In these countries, Buckwheat may frequently induce sensitisation or symptoms of food allergy or inhalant allergy in sensitised individuals (3,34-43). Approximately 5% of Korean children were reported to have IgE antibodies to Buckwheat (44). Similarly, food allergy was noted in 5.2% of Japanese students, with a higher prevalence in female students. Buckwheat was reported to be the second-most-frequent cause after Egg, followed by Shrimp, Crab, Mackerel and Cow's milk (33). In a study of the incidence of anaphylaxis in a Korean tertiary care hospital, radio-contrast media and Buckwheat were respectively the leading causes of drug and food anaphylaxis (45).

Despite being a potent allergen when ingested or inhaled, Buckwheat has been increasingly popular, in particular as a health food, in the United States, Canada, and Europe (46-47). Researchers have suggested that allergy to Buckwheat will become a larger problem as a result of its increased use in the food processing industry. Buckwheat is also used as a substitute cereal for children with coeliac disease (43).

Some authors have stated that Buckwheat can cause allergic reactions much more severe than Wheat and its relatives do, and that allergy to Buckwheat should therefore be considered in patients with classic symptoms of food allergy, where the signs are often severe (43). Symptoms include gastrointestinal distress, urticaria, Quincke oedema (angioedema), dyspnoea, rhinorrhoea, wheezing, asthma, rhinitis, anaphylaxis and shock (48-51).

Among adult asthmatics in a Japanese study, 625 of 3102 (20.1%) had a positive test to 1 or more food allergens, according to skin-specific IgE evaluation. The commonest food allergens were Shrimp (27.7%), Crab (27.7%), Yeast (23.8%) and Buckwheat (15.8%). Positive food challenge responses occurred in 30/60 subjects (50%). The foods which most often provoked a reaction were Buckwheat, Shrimp, Crab and Bread (52). In a Japanese study, more severely asthmatic children had a higher incidence of positive intracutaneous skin tests to house dust, molds, Japanese cedar tree, Ragweed, Cat dander, Silk and Buckwheat (53). An earlier study reported the opposite in children with asthma (54).

From the results of a questionnaire sent to 341 elementary school nurses in Yokohama, the incidence of Buckwheat allergy in of 92,680 children was determined to be 0.22% (140 boys and 54 girls). Symptoms were urticaria (37.3%), skin itching (33.3%), and wheezing (26.5%). Anaphylaxis was reported in 4 children (3.9%). The incidence of anaphylaxis due to Buckwheat was higher than that due to Egg and Milk allergy. Seven pupils had allergic reactions to Buckwheat noodle served at school lunch (55).

The French Allergy Vigilance Network, which monitors adverse allergy reactions in that country, reported that in 2002, 107 cases were reported, of which 59.8% were cases of anaphylactic shock, 18.7% of systemic reactions, 15.9% of laryngeal angioedema, and 5.6% of serious acute asthma. The most frequent causal allergens were Peanut (n=14), Nuts (n=16) and Shellfish (n=9). Severe adverse reactions to Buckwheat were reported in 3, in contrast to 4 to Sesame, 3 to Cow's milk, and 3 to Fish (56).

In 34 Finish children with atopic dermatitis, 33 were SPT positive to Wheat and 18 to Oats, whereas Rice, Maize, Millet or Buckwheat was positive in 16/34 patients (57).

Inhalation of very small amounts of Buckwheat allergen can initiate severe allergic symptoms (19). A 20% reduction in lung function after inhalation of aerosolised Buckwheat allergens has been documented (58). In 12 children with IgE-mediated food allergy who developed asthma on inhalational exposure to food, the implicated foods were Fish, Chick pea, Milk, Egg and Buckwheat. Bronchial food challenge resulted in 5 children showing objective clinical features of asthma and 2

developing late-phase symptoms (59). An interesting report described a young woman who experienced anaphylaxis after entering a pancake restaurant but before consuming any food or drink. Investigation demonstrated sensitisation to both Dust mites and Buckwheat, and airborne Buckwheat allergens were incriminated in the anaphylactic reaction, with a Buckwheat 2S albumin implicated as the responsible allergen (60).

In Switzerland reactions to Buckwheat are uncommon and reported to be mostly due to ingested Buckwheat in the form of pizoccheri (dumplings) and Buckwheat bread. A study described 6 individuals who experienced allergic reactions due to Buckwheat. Symptoms of urticaria were experienced by 6, angioedema in 4 and asthma in 5. Four patients reacted to ingestion of Buckwheat and 2 to inhaled Buckwheat allergens in an occupational setting. All were shown to have positive SPT and raised allergen-specific IgE to Buckwheat (49).

Exposure to Buckwheat may also result in anaphylaxis (61-62). An anaphylactic reaction was reported in a 19-year-old-man after he ate "poffertjes" (small Dutch pancakes), the principal ingredient being Buckwheat. The authors suggest that it was highly likely that this patient had been sensitised to Buckwheat by sleeping on a pillow stuffed with Buckwheat husk (63). Similarly, an individual developed asthma and worsening allergic rhinitis after exposure to Buckwheat present in his pillow. SPT and IgE *in vitro* test were strongly positive, and the later was reported to be class 4 (64). Indeed, nocturnal asthma from sleeping on Buckwheat chaff-stuffed pillows, a common type in Korea, has been reported as a result of Buckwheat allergy (65-66). However, House dust mite (*D. farinae*) may also be an important allergenic substance in Buckwheat-husk pillows (67).

A woman with asthma is described who had anaphylaxis, generalised urticaria, and an acute exacerbation of asthma 5 minutes after ingesting Buckwheat. She was markedly SPT positive for Buckwheat, and serum Buckwheat-specific IgE was reported as class 6 (32).

A 36-year-old man is described who experienced nausea, vomiting, urticaria, a sensation of throat closing, inability to speak, dyspnoea, and dizziness shortly after ingesting a large portion of Buckwheat. In the previous 2 years, he had experienced asthma, contact urticaria, allergic conjunctivitis, and allergic rhinitis from sleeping with a Buckwheat pillow. Six months after the first ingestion reaction, the patient again experienced anaphylaxis requiring emergency treatment when he accidentally ate crackers with a small amount of Buckwheat in them. SPT and IgE *in vitro* test were markedly positive for Buckwheat. The authors postulated that inhaled Buckwheat, provoking asthma, had sensitised the patient prior to the 2 episodes of ingestion anaphylaxis (46).

A 37-year-old woman twice developed a life-threatening anaphylactic reaction after eating galettes, a special French pancake from Brittany. She had tolerated ordinary pancakes and crêpes for many years. Investigation confirmed Buckwheat as the causative allergen, and found it in the galettes. SPT and IgE *in vitro* test was positive for Buckwheat. The authors suggested that whenever a patient experiences allergic reactions due to pastries, Buckwheat allergy should be considered (68).

Food-dependent exercise-induced anaphylaxis caused by Buckwheat may also occur, as reported in an 8-year-old girl. The patient consumed Buckwheat noodles called "zaru soba" and swam vigorously immediately thereafter. Approximately 30 minutes later, she complained of abdominal pain, vomiting, coughing, and chest discomfort, followed 10 minutes later by a deterioration of consciousness and cardiorespiratory arrest. An exaggerated hematemesis that occurred immediately after hospital admission indicated an inflammatory condition of the digestive tract that was caused by Buckwheat. Marked ulceration accompanied with hemorrhage and necrosis was noted at the ileum. Extensive hemorrhage involving the endotracheal pulmonary field and lymphocyte infiltration of the alveolar space likely appeared after the inflammation. The

serum IgE antibody level was raised for Buckwheat (20).

Buckwheat may also be a "hidden" allergen. Anaphylaxis as a result of Buckwheat used as filler in pepper has been reported (69); and to "hidden" Buckwheat in a Wheatburger (70).

Occupational rhinitis, conjunctivitis, asthma or urticaria may occur to Buckwheat or Buckwheat dust in animal husbandry and other food industry workers (1). These symptoms have occurred after exposure to comparatively low levels of Buckwheat dust resulting from the grinding and packaging of Buckwheat (71-72), to Buckwheat flour (73), and in a noodle maker (74-75). Occupational asthma has also been reported in an individual working in a pancake restaurant, and was confirmed by specific bronchial challenge with aerolised Buckwheat (39,50).

Other reactions

Pulmonary haemosiderosis as a result of non-immediate Buckwheat protein hypersensitivity has been reported. The patient had no skin reactivity or IgE antibodies, but was positive to a patch test (76).

Immediate hypersensitivity reactions induced by Buckwheat ingestion are considered to be IgE-mediated. Some subjects, however, develop no immediate adverse reactions after Buckwheat ingestion, despite high levels of Buckwheat-specific IgE antibodies. To elucidate the possible mechanisms, RAST inhibition between these antigens were performed using sera from 23 Buckwheat-sensitive subjects and 30 Buckwheat-tolerant subjects who had IgE antibodies for both Buckwheat and Rice. The authors report that there was cross-reactivity with IgE antibodies between Buckwheat and Rice, and that IgE antibodies from Buckwheat-tolerant subjects with high levels of IgE antibodies to Buckwheat might recognise the epitopes on Buckwheat antigens which cross-react with Rice antigens, whereas IgE antibodies from the Buckwheat-sensitive subjects might bind to Buckwheat-specific epitopes. (77)

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Anacardium occidentale

Family: *Anacardiaceae*

Source material: Shelled nuts

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Allergen Exposure

Geographical distribution

The Cashew nut comes from the Cashew nut tree, a member of the *Anacardiaceae* family, which includes a number of dermatitis-inducing plants such as poison ivy, poison oak, poison sumac and lacquer sumac. The tree is native to Brazil but is grown in other parts of the world, and the nut is now also exported from southern India, Mozambique, Tanzania and Kenya. This is a small perennial evergreen tree growing to 12 m tall, with a short, often irregularly-shaped trunk. The leaves are simple, alternate, spirally arranged, leathery, elliptic or obovate, up to 22 cm long and 15 cm broad, with a smooth margin.

The buds grow on terminal panicles which are up to 26 cm long. The flowers change from pale green to reddish as they develop and have 5 slender, pointed petals 7-15 mm long. The Cashew tree flowers once a year and pollination is mainly by insects. In the northeast region of Brazil, where the tree grows in great numbers, it flowers once a year between August and October.

The pear-shaped accessory fruit or false fruit is called the Cashew apple. This measures 4-8 cm by 10-20 cm and is yellow or red, soft and juicy, and rich in vitamin C. But the 3 cm, edible, smooth-kernelled, kidney-shaped nut (botanically defined, a seed) that grows at the end of the Cashew apple is the real fruit.

The Cashew nutshell has 3 layers. The outer leathery exocarp and the thin, hard, inner endocarp enclose a honeycombed mesocarp which is filled with an oily fluid containing substances that are themselves allergens: cardol, cardanol, 2-methylcardol and anacardic acid. This oily brown Cashew nut shell oil causes an immediate vesicant reaction because of its high concentration of phenols. Cashew wood exudes a yellow gum that also can cause vesicant reactions. It is used in the production of varnish, insect repellents, and adhesives. The tree bark produces thick resinous latex that turns black on contact with air and may result in blistering reactions on contact (1-3).

The oily substance in the shells must be removed before the nut is processed for consumption. Unaided shelling of the nuts can easily produce painful dermatitis (similar to poison-ivy rashes). The nuts are therefore usually first put through a hot bath for easy removal of the shells. The heating process causes the pericarp to burst, releasing the Cashew nutshell liquid (CNSL) and at the same time decarboxylating the anacardic

acids into less allergenic cardanols. The nuts are then centrifuged in sawdust to remove the endocarp and residual phenols. Heating, water washing and agitation constitute an alternative process (4). Next, the endocarp is removed to yield an edible nut. Raw Cashews are not processed to the same extent and may be contaminated with the shell oil (1).

The resorcinol cardol is both an irritant and an allergen, with side chains similar to the side chains of poison ivy and poison oak. Early oral exposure to resorcinols such as cardol appears to protect against contact dermatitis to catechols (present in poison ivy), whereas early cutaneous exposure to catechols predisposes to an allergic reaction to resorcinols. The concentration of phenols in the Cashew nutshell and bark is so high that contact with them causes immediate vesicant reactions. Africans have used CNSL and Cashew bark in ritual scarification and keloid formation, and it has been used for wart removal (1).

Therefore, Cashew nuts generate both allergy to Cashew nut shell oil and allergy to the nut itself. As far as the shell is concerned, roasting diffuses irritating vapours, but unless roasting is complete, not all the allergens are inactivated. Problems also arise when children play with the raw shells or when improperly shelled Cashew nuts are sold (5).

Environment

Cashew nuts are edible and popular snacks. They are also used as an ingredient in many processed foods such as nut "butters", bakery and confectionery products, and pesto. They are a common component of oriental foods.

The Cashew apple is used for its juicy but acidic pulp, which can be eaten raw or used in the production of jam, chutney, or various beverages. Its juice can also be processed and distilled into liquor or consumed diluted and sugared as a drink.

Unexpected exposure

See under Environment.

Allergens

Cashew food allergy is associated with the presence of IgE antibodies directed against the major seed storage proteins in Cashew, including the 13S globulin proteins (legumin group) and 2S albumins, both of which represent major allergen classes in several plant seeds. The 13S globulin proteins are in the 31-35 kDa range, whereas the 2S albumins are low-molecular-weight polypeptides (6). In 3 individuals who experienced anaphylaxis to Cashew nut, a number of other allergens of 15, 30 and 60 kDa were shown to be involved, the 15 kDa one possibly being a 2S albumin (7).

The following allergens have been characterised to date:

Ana o 1, a 7S vicilin-like globulin, a major allergen. (6,8-11).

Ana o 2, an 11S globulin, a 33 kDa, legumin-like protein, and a major allergen (9,11-12).

Ana o 3, a 2S albumin, a 12.6 kDa protein and a major allergen (6, 9,11,13-14).

Ana o Profilin (15).

Two isoforms of Ana o 1, Ana o 1.0101 and Ana o 1.0102, have been characterised. Ana o 1 and Ana o 3 have been expressed as recombinant allergens.

Ana o 1, a vicilin-like protein, has been shown not to share linear epitopes with Peanut vicilin. Recombinant Ana o 1 bound with 50% of sera from 20 patients with Cashew nut allergy, and with sera of 25% of 8 Cashew-tolerant patients with allergies to other tree nuts (8).

Ana o 2, a legumin-like protein, shows on immunoblots as a major band at approximately 33 kDa and a minor band at approximately 53 kDa. Legumins represent the main storage proteins in Cashew, accounting for approximately 50% of the total seed protein. Thirteen of 21 sera (62%) from Cashew-allergic patients were reactive to Ana o 2 (12).

Ana o 3 was shown to bind with sera of 21 (81%) of 26 Cashew-allergic patients (13).

A profilin has been detected in Cashew nut, at levels which may result in no clinical adverse effects (15). Its clinical relevance was not evaluated.

Potential cross-reactivity

Significant cross-reactivity has been reported between Pistachio nut and Cashew nut (13,16-17).

Cross-reactivity between Cashew nut and Walnut is possible, as a result of Ana o 2, the legumin protein which is a major allergen in Cashew nut and present in Walnut (13); and the cross-reactivity is also suggested by *in vitro* studies. A recent study described significant sequence homology between the recombinant Jug r 4 from Walnut, and Hazel nut and Cashew legumin allergens (18).

An early study reported little cross-reactivity between Cashew and Peanut or Brazil nut. (19) Although Cashew nut and Peanut vicilins share 27% identity, they were reported to not share linear epitopes, and hence did not appear to be cross-reactive (8,12,20). However, a recent study argued that the vicilin allergens of Peanut (Ara h 1), Walnut (Jug r 2), Hazel nut (Cor a 11) and Cashew nut (Ana o 1) share structurally related IgE-binding epitopes; that this epitopic community creates a risk of cross-sensitisation; and that a restriction or avoidance of tree nuts should be recommended to Peanut-sensitised individuals (10).

A 19 kDa protein from Buckwheat was reported to have weak homology to the vicilin-like allergens of Cashew, Walnut (Jug r 2), and 7S globulin from Sesamum indicum (21).

Conformational analysis of the legumin allergens of Peanut (Ara h 3), Walnut (Jug r 4), and Hazel nut (Cor a 9), along with Ana o 2 of Cashew nut, showed that consensual surface-exposed IgE-binding epitopes exhibited some structural homology. The authors suggested that individuals allergic to Peanut should avoid the other 3 nuts to prevent possible allergic reactions (14).

Pectin has been shown to contain all of the allergen epitopes of Cashew nut, whereas Cashew nut does not exhibit all of the epitopes of pectin. The clinical significance of this fact has not yet been established, and further studies are required to characterise these cross-reacting allergens (22). However, a recent study reported that Cashew nut allergy, and possibly Pistachio nut allergy, may be associated with pectin allergy, and the possibility of pectin allergy should be considered in Cashew- or Pistachio-allergic patients who have unexplained allergic reactions. The study described a 3 1/2-year-old boy who developed anaphylaxis after eating Cashew nut and later after eating a pectin-containing fruit "smoothie". The child had skin reactivity to pectin and a high level of IgE antibodies to Cashew nut and Pistachio nut, as well as a low level of IgE to Grapefruit, to which he had previously also reacted. The pectin in the smoothie was confirmed to be of citrus origin (23).

Cardol, found in the Cashew nut shell, is not usually present in the nut unless contamination occurs. An early study reported cross-reactivity of poison ivy and Cashew nut as a result of the nut being contaminated with cardol (24).

Clinical Experience

IgE-mediated reactions

Cashew nut may commonly induce symptoms of food allergy, atopic dermatitis and other hypersensitivity reactions in sensitised individuals (7,25-29). Tree nuts and Peanuts are among the most common foods responsible for causing IgE-mediated food hypersensitivity. Tree nut and Peanut allergy is usually lifelong. Cashew nut allergy may present as a singular event or in conjunction with allergy to other tree nuts.

Although typically very severe, Cashew nut allergy was initially thought to be very rare; 1 out of 1,218 in a paediatric population on the Isle of Wight, UK, was found to be Cashew nut-allergic. (26) However, Cashew nut, initially regarded as a novel food but now increasing in popularity as a snack, is regarded as an "emerging" allergen, (30) and hypersensitivity reactions are expected to increase (27). In particular, with the increasing consumption of Asian cuisine, containing foodstuffs such as Sesame, Brazil nuts and Cashew nuts, the associated allergies are more frequent than they were formerly (31).

Cashew nut allergy is now the second most commonly reported tree nut allergy in

the United States (13). Besides the protein allergens, Cashew nuts contain oleoresins which can cause contact dermatitis and are thought to cause gastrointestinal, systemic and allergic manifestations. In a French study that evaluated, using DBPCFC, 163 asthmatic and food-allergic children for food-induced asthma, Cashew nut was the ninth most frequent offending food and affected 2.1% of the group (32). The prevalence of Cashew nut hypersensitivity has also been reported to be increasing in China, as attested in a study of 30 patients with Cashew nut allergy (33). A retrospective review of 213 Australian children with Peanut or tree nut allergy reported that anaphylaxis to Cashew nut was more common than to Peanut (74.1% *vs*. 30.5%) (34).

Cashew nut allergy may span a wide age range, and age of onset may vary widely. In a study of 21 Cashew nut-allergic subjects ranging from 25 to 62 years of age, age of onset varied between 1 year and 15 years, with 15 subjects experiencing onset at less than 3 years of age (12).

In a study of 42 children with Cashew nut allergy, the mean age at the first reaction was 2 years, and the mean age at diagnosis was 2.7 years. One in 5 children (12%) had a prior history of exposure to Cashew nuts. Fifty-six per cent had skin symptoms, 25% had respiratory symptoms, and 17% had gastrointestinal symptoms. Eighteen children had proven associated food allergies (Pistachio [7], Hen's egg [5], Mustard [3], Shrimp [2], Cow's milk [1]). Eight children had positive food challenges. The study concluded that the increase in Cashew allergy is worrying because it affects young children who may have a reaction without ever having been exposed to Cashews. The authors also point out that a clinical history may be sufficiently suggestive to allow diagnosis of Cashew allergy without recourse to food challenges (35).

Significantly, minimal contact may be required to precipitate symptoms. In a study of Cashew-allergic individuals, 48% reacted to minimal contact with Cashew, *i.e.*, smelling, touching, or tasting, but not eating Cashew. The authors point out that reactions could be as severe as those from Peanut allergy (36).

Oral allergy has been described in a 26-year-old woman, who experienced tingling on her tongue and itching both in the throat and on the face immediately after she put a Cashew nut onto her tongue. SPT and serum IgE antibody tests were positive for Cashew nuts and negative for Peanuts and other tree nuts. Skin reactivity for Cashew nuts normalised one year after she began avoiding Cashew nuts (37).

Life-threatening anaphylactic reactions to Cashew nut have been reported, and one study reported on 15 subjects (6). Anaphylaxis to Cashew nut was reported in a 20-month-old girl who developed facial angioedema and generalised urticaria immediately after eating a Cashew nut; in a 12-year-old girl who experienced oral itching, generalised urticaria, wheezing, dyspnoea, and dizziness 15 minutes after eating a single Cashew nut; and in a 36-year-old woman who developed generalised erythema, rhinorrhoea, dyspnoea, dysphagia, nausea, vomiting and diarrhoea immediately after eating ice cream containing Cashew nut. SPT and IgE antibodies to Cashew and Pistachio nuts were positive in all 3 patients (7). A 42-year-old patient allergic to Pistachio who had anaphylaxis to Cashew nuts was described. Symptoms included mouth and lip itching, slurred voice, dyspnoea and vomiting a few minutes after eating some Cashew nuts. History disclosed 3 previous episodes of adverse reactions to Pistachio. Allergen-specific IgE was negative for both (38).

A 2007 report from Holland points out that in recent years there has been an increasing number of patients with an anaphylactic reaction after eating small amounts of Cashew nut. The report describes a boy aged 7 and 2 girls aged 9 and 10 years, with heterogeneous case histories involving allergic upper airway and conjunctival symptoms and constitutional eczema, who presented with anaphylactic symptoms after ingestion of nuts. Allergy to Cashew nut was diagnosed in the first 2 and for Peanut in the third (29).

Cashew nut is reported to cause more severe reactions than Peanut. In a study to confirm this, children whose worst-ever reaction was to Cashew nut were matched with 2 children each whose worst-ever reaction was to Peanut, resulting in a total of 47 children in the Cashew group being matched to 94 in the Peanut group. There were no differences in overall clinical features between groups, except for asthma, which was more prevalent in the Peanut group. Wheezing and cardiovascular symptoms were reported more frequently during reactions in the Cashew group, compared with the Peanut group. Furthermore, the Cashew group had received intramuscular adrenaline more frequently. The authors concluded, by using case-matching, that severe clinical reactions occur more frequently in Cashew than in Peanut allergy (39).

Inhalation of pectin has been identified as a cause of occupational asthma. The following study describes the first known case of allergy to ingested pectin. A 3 1/2-year-old boy developed anaphylaxis once after eating Cashew nut and later after eating a pectin-containing fruit "smoothie". Significant levels of IgE antibodies for Cashew and Pistachio were demonstrated, along with skin reactivity for pectin. The pectin in the smoothie was confirmed to be of citrus origin, and the authors report cross-reactivity between pectin and Cashew (23).

Anaphylactic reactions may not always be obviously attributable to Cashew nut, in particular when the nut is hidden in a compound food. For example, fatal anaphylactic reactions reported in 2 adolescents had very different but in both cases cryptic causes: a sandwich containing Cashew nut, and candy. (40) A report was made of an allergic reaction to Cashew that resulted in upper airway obstruction and was initially misdiagnosed as foreign body aspiration. (41) Cases of "idiopathic" anaphylaxis may in fact result from inadvertent contact with Cashew nut (42).

An anaphylactic reaction to Cashew nut was reported in a non-atopic 60-year-old man 25 days after he received a liver allograft from a 15-year-old atopic boy who died of anaphylaxis after Peanut ingestion. The liver recipient had no history of nut allergy. Post-transplantation skin prick test results were positive for Peanut, Cashew nut, and Sesame seed, and the donor had allergen-specific IgE antibodies to the same 3 allergens. The authors stated that this case illustrated that transfer of IgE-mediated hypersensitivity can occur after liver transplantation, with potentially serious consequences (43).

Atopic dermatitis and allergic contact dermatitis (3-4,44-48) from ingestion of or contact with Cashew nut have frequently been reported, as well as from contact with the nut shell (49). Hypersensitivity may result from contact with the urushiol present in the shell and contaminating the nut, or from the Cashew nut protein. Allergic contact dermatitis to Cashew nut may simulate photosensitivity eczema (50). Furthermore, Cashew nut dermatitis should be a consideration for individuals travelling to countries where Cashew nut is a frequent ingredient in food (51).

In an American study of 165 patients aged 4 months to 22 years with atopic dermatitis, 7 foods (Cow's milk, Hen's egg, Peanut, Soy, Wheat, Cod/Catfish, Cashew) accounted for 89% of the positive challenges (25).

Other reactions

Pollen from the Cashew nut tree may result in sensitisation, asthma and allergic rhinitis. In a study of 80 Brazilian subjects with allergic asthma, as documented by previous positive skin test reactions to various pollens, all 80 were shown to have significant skin reactivity to pollen from this tree. The authors suggested a correlation between the Cashew tree flowering period and an increased number of allergic asthma cases (52). Similarly, in an Indian study of 65 subjects with allergic asthma, 26 (40%) had positive SPT to pollen of this tree. Bronchial provocation tests were performed in 22 of the 26 patients, and 20 (90.9%) had a positive result. Allergen-specific IgE for Cashew tree pollen was raised (53).

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The urushiol dermatitis caused by plants of the *Anacardiaceae* family is the most common cause of acute allergic contact dermatitis and systemic dermatitis. Urushiol, containing cardol and ancardic acid, is found in Cashew nut shell oil. A study of 54 individuals who developed a poison ivy-like dermatitis 1 to 8 days after eating imported Cashew nuts (contaminated by urushiol from the Cashew shell oil) described how the patients had a very pruritic, erythematous, maculopapular eruption that was accentuated in the flexural areas of the body. Three had blistering of the mouth, and 4 had rectal itching. Nine who reacted to the Cashew extract also reacted to poison ivy urushiol (54).

Systemic contact dermatitis to raw Cashew nut found in imported pesto sauce has been described. In this instance, the cause was attributed to the nut shell oil's cardol and anacardic acid. The clinical expressions were dermatitis with flexural accentuation, typically distributed on the extremities, groin, and buttocks, and occurring generally 1 to 3 days after ingestion of raw Cashew nuts contaminated with allergenic oil (3).

Urushiol dermatitis has been described following the ingestion of homemade Cashew nut butter contaminated by Cashew nut shell oil, which resulted also in perianal contact dermatitis. The severe systemic dermatitis required 3 weeks of systemic steroid therapy. The authors state that perianal eruptions may be due to materials deliberately applied to the anogenital region or to ingested antigens that remain sufficiently intact within the faeces to affect perianal skin (55).

In a series of patients with Cashew nut dermatitis, patch tests were positive to moistened, crushed raw Cashews but not to roasted Cashews in patients with an internal-external contact type of hypersensitivity to raw Cashews purchased from organic food stores. Control patients without a history of poison ivy sensitivity did not react to the raw Cashew patch test and did not develop the rash on ingestion of large amounts of raw Cashews. Affected patients had eaten between 150 and 450 g of Cashews, prompting the authors to conclude that large quantities of allergen in raw Cashews would provoke the syndrome in highly sensitive people (3). (Other studies have demonstrated that very low levels of allergen are required as a trigger, suggesting that these cases involve a protein allergen, whereas in the cases in which high levels are required for a reaction, the reaction is to a substance such as cardol (4)).

With the precautions taken today to avoid contamination of food products with Cashew urushiols, it is rare to find a case of Cashew nut dermatitis as a result of urushiol in the United States (55).

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Cicer arietinus

Family: *Fabaceae* (*Leguminosae*)

Common names: Chick pea, Garbanzo bean, Bengal Gram

Source material: Dried peas

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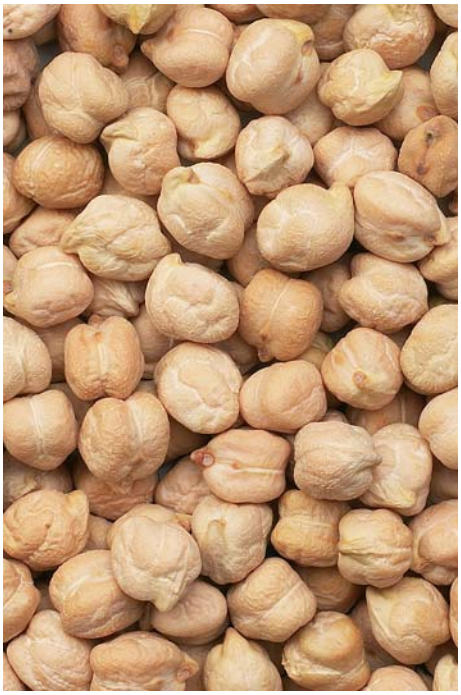
Allergen Exposure

Geographical distribution

Chick pea is a leguminous plant which produces hazel nut-shaped, nut-flavoured seeds. Chick pea is an important source of proteins, carbohydrates, B-group vitamins and certain minerals, particularly to the populations of developing nations. India contributes over 75% of the Chick pea production in the world. In India itself, this legume is consumed mostly as dhal, whole seeds, and several types of traditional, fermented, deep fried, sweetened, and puffed products. Chick peas are a staple food in the Middle East. Chick peas are also used extensively in the Mediterranean, especially in Spain. The use of Chick peas has spread along with ethnic cuisines.

Environment

The Chick pea is unknown in the wild, though there are some related wild species. Chick peas are available canned, dried and sometimes fresh. Chick pea seeds are eaten fresh as green vegetables; parched, fried, roasted, and boiled; and as a snack food, sweet and condiment. Hummus is an especially popular Chick pea recipe. Seeds are roasted and ground and the flour can be used in soup, as dhal (which has a number of uses as an ingredient), and to make bread. Sprouted seeds are eaten as a vegetable or added to salads. Young shoots and green pods are eaten like spinach (but may be toxic: see under Other reactions). A small proportion of Chick pea is used to produce fermented food. The roasted seed or root can be used as a coffee substitute. Acid exudate from the seedpod can be eaten as a type of vinegar.



The acid exudate is astringent. It has been used in the treatment of a number of ailments, including diarrhea.

Unexpected exposure

Parts of the plant can serve as animal feed, and can be made into adhesive, dye, and starch.

Allergens

Immunoblot analysis has demonstrated that 70, 64, 35, and 26 kDa proteins are major allergens (1-2). Other studies have detected multiple allergens in both raw and boiled Chick pea extracts in the molecular weight range of 10-106 kDa, of which the majority were heat-stable (3-4).

The following allergens have been characterised:

Cic a 2S Albumin, a 10-12 kDa protein (5).

Cic a IFR, an Isoflavone Reductase (6).

The presence of an allergen belonging to the profilin family has been suggested by a study examining the possible association of

oral allergy syndrome with Plane tree pollen (*Platanus acerifolia*) (7). This has been questioned by another study (8).

A beta-1,3-glucanase and two chitinases have been isolated from Chick pea. One of the chitinases, a 32 kDa protein, was shown to be a class I chitinase, and the second, a 28 kDa protein, showed homology to class III chitinases (9). The allergenic significance of these proteins has not yet been determined.

Infection of the Chick pea plant was shown to initiate the formation of a thaumatin-like protein in Chick pea leaves (10). Whether this protein occurs in the seed of the plant or whether it has allergenic potential has not been determined yet. Also, a trypsin and chymotrypsin inhibitor has been isolated in Chick pea (11). The clinical significance of this has not yet been determined.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Fabaceae* (legume family) could be expected but in fact does not occur frequently (12). In an early study, an *in vitro* study, the specific IgE binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked between the extracts of Peanut, Garden pea, Chick pea, and Soybean (13.) Legumes have a high degree of immunological cross-reactivity, at least in *in vitro* studies. The allergenicity of legumes is mainly is mainly related to allergens from the storage proteins of seeds. Vicilins from this group of proteins could be an important common allergen in clinical allergy to legumes. Other panallergens of increasing importance are lipid transfer proteins (14). However, some clinical studies have reported that there is little cross-reactivity between members of the legume family (15-16).

In fact, although the different legumes have structurally homologous proteins, they are not all equally allergenic, thus making it difficult to distinguish *in vitro* and *in vivo* cross-reactivity. Studies in Spanish patients, in whom a high prevalence of chick pea allergy occurs, have shown that most of the patients are sensitised to more than one species. A great degree of cross-reactivity was demonstrated among Lentil, Chick pea, Pea and Peanut by inhibition studies. The authors report that unlike the Anglo-Saxon population, this phenomenon implies clinical sensitisation for many Spanish children and that the majority of these patients have had symptoms with more than one legume (median 3 legumes). Of 39 patients challenged with two or more legumes, 32 (82 %) reacted to two or more legumes: 43,5 % to 3, 25,6 % to 2, 13 % to 4 legumes. Seventy three per cent of the patients challenged with Lentil and Pea had positive challenge to both, 69,4 % to Lentil and Chick pea, 60 % to Chickpea and 64,3 % to Lentil, Chick-Pea and Pea simultaneously. Peanut allergy was associated with to allergy to Lentil, Chick pea and Pea but less frequently, whereas White bean and Green bean and Soybean were well tolerated by children allergic to other legumes. The authors stressed that in spite of an evident clinical and immunological cross-reactivity, the diagnosis of legume allergy should not be based only on allergen-specific IgE tests (17).

Nevertheless, some reports of specific cross-reactivity between certain members of this family have been published. Lentils appear to be cross-reactive with Chick pea and beans (4,18-19), and cross-reactivity was shown between Pea, Soybean, White bean, Peanut, Lentil, Fennel, Guar gum, Carob bean, Tragacanth, Chick pea and Liquorice (20).

Of 720 patients evaluated for oral allergy syndrome (OAS), and sensitisation to Plane tree (*P. acerifolia*) pollen, 61 (8.48%) were sensitised to pollen from this tree, and food allergy was reported in 32 (52.45%) of these 61 patients. The food allergens most frequently implicated were Hazel nuts, Peach, Apple, Peanuts, Maize, Chick pea and Lettuce. The study concluded that cross-reactivity was observed between *P. acerifolia* pollen and plant-derived foods, and that OAS in these patients may have been caused by primary respiratory sensitisation to Plane tree pollen. The authors suggested that profilin may be the responsible allergen (7).

Cross-reactivity between allergens from Latex and Chick pea was recently described in a boy with spina bifida with allergy to Chick pea, which developed after the appearance of Latex allergy symptoms. IgE antibodies to Latex and Chick pea were demonstrated by SPT and serum IgE antibodies (21).

In a Spanish study, symptomatic hypersensitivity to Chick peas was frequently associated with Lentil allergy (22). In another Spanish study, aimed at determining the prevalence of Lupin sensitisation in 1,160 subjects consulting allergologists, a 4,1 % sensitisation rate (28 patients) was found, with 75% co-sensitisation between Lupin and legumes. Of 28 patients, 13 were shown to have skin reactivity to Chick pea, 8 to Pea, 12 to Peanut, 13 to Bean, and 7 to Lentil (but 18 were not tested for Lentil) (23).

Clinical Experience

IgE-mediated reactions

Chick pea may commonly induce symptoms of food allergy in sensitised individuals, in particular in communities where this legume forms part of the staple diet such as India, in the Mediterranean area and Middle East. The clinical manifestations of the allergy to Chick pea are similar to that for all legumes ranging from oral allergy syndrome, urticaria, angioedema, rhinitis, asthma, to anaphylaxis and death (13,24).

Legumes are an important ingredient in the Mediterranean diet. In the Mediterranean area and Middle East, the most commonly consumed legumes are Lentils and Chickpea. (In the United States, United Kingdom and south-east Asia, the major legumes involved in food allergy are considered to be Peanut and Soy bean) (13). Among Spanish children, sensitivity to legumes is the fifth most prevalent food allergy. Lentil and Chick pea are the most frequent cause of allergic reactions to legumes in Spanish children (16) but this may vary from one geographical area to another: in a study of food allergy in 674 patients referred to an Allergy Unit in Spain, the prevalence of food legume allergy was 9.1%. Two patients were challenge-positive to Chick pea (25).

Chick pea has been reported to be an important allergen in India. Of 1,400 patients screened for Chick pea allergy, 142 were food allergy-positive on history, of which 59 implicated Chick peas. Subsequent challenges demonstrated that 31 were DBPCFC-positive for Chick pea (2). Further reports from India indicate that Chick pea is an important source of allergens that can cause IgE-mediated hypersensitivity reactions ranging from rhinitis to anaphylaxis. The ELISA results did not correlate well with the DBPCFC results; however, the skin test results correlated with DBPCFC in 75% of patients (1).

Other symptoms reported from Chick pea allergy include urticaria, angioedema, abdominal symptoms, rhinoconjunctivitis and/or asthma, which may follow ingestion or inhalation of vapours from cooked Chick pea and other cooked legumes (Lentil, bean). Lentil was found to induce the most severe reactions (26). Other studies have also implicated Chick pea in the genesis of allergic symptoms following inhalation. Twelve children with an IgE-mediated food allergy who developed asthma on inhalational exposure to food were identified in one study. The implicated foods were Fish, Chick pea, Milk, Egg and Buckwheat. Nine out of the 12 children consented to undergo a bronchial food challenge, of which 5 challenges were positive, with objective clinical features of asthma. Additionally, two children developed late-phase symptoms, with a decrease in lung function. Positive reactions were seen with Fish, Chick pea and Buckwheat (27). Allergic reactions to legumes through inhalation have also been described in adults, notably a 20-year-old man who experienced asthmatic attacks when exposed to the steam from cooking either Chick pea or Lentil. Type I hypersensitivity to the antigens in these legumes was demonstrated by means of immediate skin reactivity, histamine release tests, IgE antibody determinations and RAST inhibition. Specific bronchial challenges with the heated (75 °C for 30 min)

extracts of Chick pea and Lentil elicited isolated immediate responses (4). A 20% reduction in lung function after inhalation of aerosolised Fish, Buckwheat and Chick pea has been reported (28).

Importantly, Chick pea allergens appear to be heat-stable. Sera of 29 children with a history of allergic reactions after ingestion of Chick pea, and positive skin tests to this legume, were used to study the allergenic composition of raw and boiled Chick pea extracts. There were no significant differences between IgE antibody levels to the raw and boiled extracts. Patients with a current clinical allergy to Chick pea were shown to have statistically higher IgE antibody levels than tolerant patients and controls (3).

Reactions to Chick pea may be severe. An 8-year-old girl suffered with contact urticaria from raw Chick peas and an anaphylactic reaction after ingestion of cooked Chick peas (29). Anaphylactic reactions have been described by other authors (1). Features of anaphylaxis including severe wheezing and urticaria occurring 1 hour after the ingestion of Chick pea were reported in an 8 year old Indian girl. She had a previous history of wheezing following inhalation of chick pea flour or its vapours emitted while being cooked. External application of chickpea paste had resulted in urticaria. Specific IgE to Chick pea was detected both in serum and in skin (30).

Occupational exposure may result in allergic reactions. Asthma has been reported in individuals exposed to vapours from cooking of some kinds of legumes (Peas, Chick peas, beans, Lentils) (31). Also reported was the case of a 20-year-old man who experienced asthmatic attacks when exposed to the steam from cooking either Chick pea or Lentil. Type I hypersensitivity to the antigens in these legumes was demonstrated by means of immediate skin reactivity, histamine release tests, IgE antibody determinations and RAST inhibition (4).

Other reactions

The foliage and seedpods contain oxalic acid and can irritate the skin. Oxalic acid can lock up certain nutrients in the diet, especially calcium, and therefore heavy use of foods that contain this substance can lead to nutritional deficiencies. Cooking will greatly reduce the oxalic acid content. People with a tendency to rheumatism, arthritis, gout, kidney stones or hyperacidity should take especial caution if including this plant in their diet, since the oxalic acid can aggravate their condition.

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f36 Coconut

Allergen Exposure

Geographical distribution

The Coconut is native to tropical eastern regions, but today it is also grown in the tropical parts of the United States, in Central and South America, and in Africa. The largest-producing countries are Mozambique, Tanzania and Ghana. Coconut is a staple food in Asia. Coconuts are both a main source of income for many producing countries, and a source of many important products used in the industrialised world.

The Coconut palm is a long-lived, single-trunk plant up to 30 m tall, with a spiky to drooping crown of long leaves at the top. The fruit, as big as a man's head and 1-2 kg in weight, is a drupe with a thin, smooth, grey-brownish epicarp, a fibrous mesocarp and a woody endocarp. Inside, it contains a single seed, which is partly liquid (Coconut milk) and partly solid (Coconut meat).

Environment

Man can use every part of the Coconut. Coconut can be harvested when young, but the mature fruit is more familiar to the West.

Cocos nucifera

Family: *Arecaceae*

Common names: Coconut, Common Coconut

Source material: Fresh coconut meat

There have in the past been 60 other species classified under the genus *Cocos*, but the Coconut palm is actually monotypic, meaning that within the genus *Cocos* only one species, *nucifera*, is now recognised, though within this species are numerous varieties

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The white nut-meat can be eaten either raw or cooked, alone or in a great variety of dishes. The sap produces palm wine and vinegar. The apical buds are eaten as "palm-cabbage". Coconut milk derives from the unripe nuts and is used fresh or fermented. Desiccated Coconut consists of dried and shredded endosperm. Though desiccated Coconut meat in sweets and pastries is the most visible use of Coconut in the West, the oil is very widely used in processed foods such as margarine. Coconut is sensitive to oxidation due to the high oil content and should be stored in well-sealed containers.

At one time, Coconut oil received negative press because of its high level of saturated fat. However, recent research has shown that the fatty acids in unhydrogenated Coconut oil, the medium-chain triglycerides, do not raise serum cholesterol or contribute to heart disease, as do the long-chain triglycerides found in seed oils.

Coconuts are high in protein. Additionally, they have been classified as a "functional food", providing health benefits beyond those from the basic nutrients. The lauric acid in Coconut oil is converted into monolaurin in the body. Monolaurin is the antiviral, antibacterial, and antiprotozoal monoglyceride that destroys lipid-coated viruses and various pathogenic bacteria in the body. Studies have also shown some

antimicrobial effects of free lauric acid. Coconut oil is also used by hypothyroid sufferers to increase body metabolism and to lose weight.

Non-edible parts of the plant are used for thatch, fertiliser, charcoal, lumber, caulking, components of furniture, tools, gas masks and air filters, and material for basket-weaving and many other handicrafts. Coconut oil may be burned for illumination and is often used for making natural soaps and other health products, detergents, etc.

Unexpected exposure

See under Environment and Other reactions.

Allergens

Coconut allergens appear to be 55, 35, and 36.5 kDa in size. The 35 kDa Coconut protein was shown to be immunologically similar to Soy glycinin (in the legumin group of seed storage proteins) (1).

In a 28-year-old man who experienced anaphylaxis following ingestion of Coconut ice-cream, protein bands of 15, 20, 35, 45 and 200 kDa were detected. IgE immunoblot showed intense reactivity to a 78 kDa protein, and weaker bands for 15-20, 22 and 30 kDa proteins (2).

In a study of a patient with anaphylaxis to Coconut and oral symptoms to tree nuts, IgE binding to 35 and 50 kDa protein bands in Coconut and Hazel nut extracts, respectively, was demonstrated (3).

The serum of a 64-year-old woman, who was monosensitised to Coconut, demonstrated multiple allergen-specific IgE-reacting bands to Coconut milk and Coconut pulp, as well as to dry commercial Coconut powder. The most prominent proteins involved had an apparent molecular weight of 18, 22 and 28 kD (4).

An IgE binding protein of about 18 kDa and 2 weaker bands of about 25 and 75 kDa were demonstrated in the serum of a 3-year-old boy who presented with abdominal pain, vomiting, oral allergy syndrome, and oedema of the eyelids immediately after ingesting a Coconut (5).

The following allergens have been isolated:

Coc n 7S globulin (6-7).

Coc n 11S globulin, known as Cocosin (6,8).

Coc n Profilin has been isolated from Coconut tree pollen (9).

A report was made of 2 Coconut-allergic patients, a 30-year-old man who experienced severe oropharyngeal itching, throat hoarseness, and gastric pain; and a 4-year-old girl who experienced anaphylaxis. An almost identical profile of IgE binding proteins in the Coconut extract was demonstrated in both patients. Both reacted strongly to a band of approximately 29 kDa, shown to be a 7S globulin (7). The 29 kDa band was digested by pepsin in less than 1 minute.

Coconut water contains the proteins glutelin and prolamin (10). Their allergenic potential has not been assessed.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (11).

A 35 kDa Coconut protein is immunologically similar to Soy glycinin (in the legumin group of seed storage proteins). In 2 patients allergic to Coconut, the clinical reactivity was reported to likely be due to cross-reacting IgE antibodies primarily directed against Walnut, the original clinical allergy reported, and most likely against a Walnut legumin-like protein (1). Coconut only partially inhibited IgE reactivity to 35 and 36 kDa bands on a Walnut immunoblot, suggesting that IgE resulting from primary Walnut exposure was responsible for a secondary cross-reaction to Coconut (12). Even though Coconut is a monocot and Walnut a dicot, a quite distant relationship, evidence of substantial IgE cross-reactivity between the 2 nuts was detected (12). Similarly, cross-reactive allergens between Hazel nut (a tree nut) and Coconut (a distantly related palm family member) have been reported (3).

In a report on 2 Coconut-allergic patients, a 30-year-old man who experienced severe oropharyngeal itching, throat hoarseness, and gastric pain, and a 4-year-old girl who experienced anaphylaxis, both reacted strongly to a band of approximately 29 kDa shown to be a 7S globulin, a protein with a high correlation with a 7S globulin from Elaeis guineensis (Oil Palm). Cross-reactivity was demonstrated among Coconut, Walnut, and Hazel nut by inhibition studies in patient 2 (7).

There may be a weak association between Latex allergy and allergy to Coconut. Among 137 patients with Latex allergy, 49 potential allergic reactions to foods were reported in 29 (21.1%). Foods responsible for these reactions included Banana (n=9, or 18.3%), Avocado (n=8, or 16.3%), shellfish (n=6, or 12.2%), fish (n=4, or 8.1%), Kiwi (n=6, or 12.2%), and Tomato (n=3, or 6.1%); Watermelon, Peach, and Carrot (n=2, or 4.1% each); and Apple, Chestnut, Cherry, Coconut, Apricot, Strawberry, and Loquat (n=1, or 2.0% each). Reactions to foods included local mouth irritation, angioedema, urticaria, asthma, nausea, vomiting, diarrhoea, rhinitis, and anaphylaxis (13).

Clinical Experience

IgE-mediated reactions

Coconut may uncommonly induce symptoms of food allergy in sensitised individuals (1,14-16). The prevalence of Coconut allergy has not been studied; however, the Food Allergy and Anaphylaxis Network (FAAN) Peanut and Tree Nut Allergy Registry in the USA, which collected data on 5,149 patients (mainly children), records that 4 individuals reported allergy to Coconut (17).

A baby of 8 months, fed from birth with maternal milk, developed severe gastro-intestinal symptoms due to the presence of Coconut oil in an infant formula. Diagnosis was made using SPT and oral challenges (18).

A report described 2 Coconut-allergic patients: a 30-year-old pollen-allergic man monosensitised to Coconut who presented with severe oropharyngeal itching, throat hoarseness, and gastric pain 10 minutes after the intake of fresh Coconut; and a 4-year-old girl with a previous allergy to Walnut (intense oropharyngeal itching and facial pruritic erythema after ingesting a small amount of Walnut), but not allergic to pollen, who developed anaphylaxis on Coconut ingestion. Within 15 minutes of eating a piece of fresh Coconut, she experienced intense oropharyngeal itching, followed by facial angioedema, cough, wheezing and dyspnoea requiring emergency treatment. Both patients were shown to have skin reactivity and serum IgE to Coconut. The adult patient did not report any adverse reactions Peanut or tree nuts. For him, Coconut-specific IgE was 18 kU_A/l. The young girl's IgE was 18.3 kU_A/l for Coconut, and IgE for Almond, Hazel nut, and Walnut were 2.40, 19.70, and 49.0 kU_A/l, respectively, with cross-reactivity being demonstrated between these (7).

Monosensitisation to Coconut was described in a 64-year-old woman who experienced generalised urticaria, facial and uvula oedema, dysphagia and dyspnoea a few minutes after eating a Coconut biscuit. She also experienced bronchoconstriction, hypotension and hypoxemia minutes after eating a Spanish sweet containing, among other ingredients, Coconut. She was not sensitised to the other ingredients. SPT was strongly positive for Coconut pulp and Coconut milk, and a skin reaction (oedema and erythema) developed 4-6 hours later. No skin reactivity was demonstrated for, among other substances, Date, Palm pollen, Peanut, Almond, Pistachio nut, Walnut, Hazel nut, Sweet chestnut, Soybean, Cocoa, Chick pea, Lentil, Mustard or Latex. Coconut IgE antibody level was 20.8 kU_A/l, but not detected for Tree nuts, legumes or Soybean (4).

A 3-year-old boy was described as experiencing abdominal pain, vomiting, oral allergy syndrome, and oedema of the eyelids immediately after ingesting a Coconut sweet. A year after this episode, he experienced the same symptoms after eating a small portion of fresh Coconut. SPT to Coconut with fresh Coconut was strongly positive. SPT was weakly positive for Almond, and an oral challenge with Almond was negative. A patch test with Coconut was negative. Coconut-specific IgE was Class 3 (5).

Two patients aged 50 and 21, with tree nut allergy manifested by life-threatening systemic reactions, reported systemic reactions after the consumption of Coconut. The clinical reactivity in these 2 patients was ascribed to cross-reacting IgE antibodies directed primarily against Walnut, the original clinical allergy reported, and most likely against a Walnut legumin-like protein (1).

Anaphylaxis following the ingestion of Coconut has been reported in a 28-year-old atopic man following ingestion of Coconut ice cream. The reaction consisted of oral pruritis, vomiting and intense angioedema of the lips and uvula (2).

Concomitant anaphylaxis to Coconut and oral symptoms to Hazel nut have been reported, with positive SPT to Coconut (3).

Contact dermatitis to Coconut has been more commonly reported than Coconut food allergy. Coconut-derived products include Coconut diethanolamide, cocamide sulphate, cocamide DEA, and CDEA. These are commonly present in cosmetics, moisturisers, soaps, hand washing liquids and other cleansers, and shampoo. An itchy, blistering rash may arise a day or two after contact with the allergen and take several days to resolve - unless ongoing contact with the allergen is made, in which case it will persist (19).

It has been proposed that sensitisation to foods may occur through topical exposure. A study sought to describe the prevalence of allergenic foods and herbs in pediatric skin care products and found that Coconut was the most common food present. It was found in 44.4% of the products examined, and was particularly often used in soaps and body washes (75.9%) and in shampoos (76.9%) (20).

Other reactions

Various substances, *e.g.*, Coconut diethanolamide (CDEA), are manufactured from Coconut and Coconut oil. These substances are widely used as surface-active agents in hand gels, hand-washing liquids, shampoos and dish-washing liquids, and may result in contact dermatitis (19,21).

Pollen from the Coconut tree has been reported to result in rhinitis and asthma in Coconut pollen-sensitised individuals (22-24).

Occupational allergic conjunctivitis due to Coconut fibre dust was reported in a 46-year-old who had worked for 10 years in a Coconut fibre mattress factory. Conjunctivitis would develop 20-30 minutes after he began tufting mattress with Coconut fibre (25).

f36 Coconut

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Panicum milliaceum

Family:	*Poaceae* (*Gramineae*)
Common names:	Common millet, Prove millet, Broomcorn Millet, Broom-corn millet, Hog millet, Russian millet, Brown corn
Source material:	Peeled seeds
See also:	Foxtail millet f56 and Japanese millet f57

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Allergen Exposure

Geographical distribution

The name Millet is used to describe seeds from several taxonomically divergent species of grass. They are grown mostly in marginal areas and under agricultural conditions in which major cereals fail to give sustainable yields (3).

See common background for Millets on next page.

Common millet and the other Millets are not closely related to Wheat. Common millet was grown in prehistoric Europe. Because of its ability to mature quickly, it is often cultivated by nomads. This shallow-rooted plant varies in height between 30 and 100 cm. The grain contains a comparatively high percentage of indigestible fibre because the seeds are enclosed in the hulls and are difficult to remove by conventional milling processes (1).

Environment

See common background for Millets on next page.

The Millets are important sources of food for humans and animals. But in the West, with the exception of natural food stores, Millet is sold mainly as bird feed.

Unexpected exposure

See common background for Millets on next page.

Allergens

No allergens from this plant have yet been characterised.

In a study of 7 patients who experienced allergic symptoms after ingestion of Millet, immunoblotting detected 3 major allergens in Millet extract, directed to serum IgE antibodies of 6 of the patients. In the control group, 10 of 16 (63%) of Millet-exposed atopic bird keepers were shown to have IgE antibodies directed at allergens in Millet extract. A protein of approximately 36 kDa was recognised by 94% of the patients. An allergen of approximately 70 kDa was recognised by 62% of the patients, and an allergen of approximately 90 kDa by 75% of the patients (4).

In a study, the antigenic relationships among “minor Millets” (Barnyard, Little and Foxtail millets) and other cereals

f55 Common millet

Common background for Millets

The Millets are not a taxonomic class, but rather a functional one. They are all small-seeded grasses viable in harsh climates, and they are often used for fodder and food.

The Millet species span several genera, most notably in the subfamily *Panicoideae*, of the grass family *Poaceae*. The following are the most widely cultivated species, shown in these tables in order of worldwide production volume (1).

Table 1a. Origins and common names of Millets.

Common name	Crop	Other Common names	Suggested origin
Sorghum	*Sorghum bicolor*	Great millet, guinea corn, kafir corn, aura, mtama, jowar, cholam. kaoliang, milo, milo-maize	Northeast quadrant of Africa (Ethiopia-Sudan border)
Pearl millet	*Pennisetum glaucum*, *synonym Pennisetum americanum*	Cumbu, spiked millet, bajra, bulrush millet, candle millet, dark millet	Tropical West Africa
Foxtail millet	*Setaria italica*	Italian millet, German millet, Hungarian millet, Siberian millet	Eastern Asia (China)
Common millet	*Panicum miliaceum*	Proso millet, hog millet, broom-corn millet, Russian millet, brown corn, white millet	Central and eastern Asia
Finger millet	*Eleusine coracana*	African millet, koracan, ragi, wimbi, bulo, telebun	Uganda or neighbouring region

Table 1b. Minor millets include:

Barnyard millet	*Echinochloa crus-galli*	Sawa millet, Japanese barnyard millet	Japan
Kodo millet	*Paspalum scrobiculatum*		India
Little millet	*Panicum sumatrense*		Southeast Asia
Guinea millet	*Brachiaria deflexa, synonym Urochloa deflexa*		Guinea
Browntop millet	*Urochloa ramose, synonyms Brachiaria ramose, Panicum ramosum*		South East Asia

Modified from: Food and Agriculture Organization of the United Nations Sorghum and millets in human nutrition. ISBN 92-5-103381-1. www.fao.org/DOCREP/T0818e/T0818E01.htm Accessed April 2008.

Teff (*Eragrostis tef*) and Fonio (*Digitaria exilis*) are also often classed as Millets; more rarely, Sorghum (*Sorghum spp.*) and Job's tears (*Coix lacrima-jobi*) are called Millets. Teff, however, which is common in Ethiopia, is not a true Millet. Fonio (*Digitaria exilis*), though a Millet, is of minor importance (1). Some experts regard Sorghum as a Millet; this would make it the most productive Millet variety (2).

For centuries, Sorghum and Millet have been staple foods in the semi-arid Asian and African tropics. For millions of the poorest inhabitants of these places, there is no more important source of energy, protein, vitamins and minerals. The crops grow in harsh climates and poor soil, with little fertiliser or other inputs. As classic subsistence crops, they are usually consumed by the growers rather than traded. However, in the West they are increasingly valued as “natural foods”, which has meant wider commercial availability and a greater variety of uses worldwide.

The basic kernel structure, with pericarp, germ or embryo, and endosperm, is the same for Sorghum and the various Millets. The largest part of the kernel is the endosperm, used for storage. In Foxtail and a few other Millets, the pericarp is like a bag, attached to the endosperm at a single point. In Millets and Sorghum, the aleurone layer of the pericarp, located just below the seed coat, is rich in minerals, B vitamins and oil, and includes some hydrolysing enzymes. Alcohol-soluble prolamins are the most abundant proteins. There are also albumin and globulin, cross-linked prolamin and other glutelin-like proteins. Millet and sorghum do not contain gluten.

(Wheat, Maize, Rice, Sorghum, Finger millet and Pearl millet) were evaluated using an antibody raised against a 20 kDa prolamin from Kodo millet. It was demonstrated that this prolamin was related to the prolamins from the other foods. Rice was the only common cereal that did not cross-react immunologically with the 20 kDa prolamin of Kodo millet (5). Common millet was not assessed, and it is possible that a similar protein is present in Common millet.

A Rice protein of 16 kDa was reported to be involved in cross-allergenicity among antigens in Rice, Wheat, Corn, Japanese millet and Foxtail millet (6). This protein was subsequently shown to have sequence homology to Wheat alpha-amylase inhibitor and Barley trypsin inhibitor (7). Common millet was not assessed, and it is possible that a similar protein is present in Common millet.

A beta-amylase of 58 kDa, belonging to a protein family that has allergenic members, was isolated from germinating Common millet seed (8). The allergenicity of this protein was not evaluated.

Potential cross-reactivity

Studies have not reported cross-reactivity between Millet and Barley, Maize, Oats, Wheat, or grass pollen (Rye, Orchard, and June grass) (2,9-10). A study found that though cross-reactivity to these cereals may be suggested by the presence of IgE antibodies directed to them, this was not clinically relevant (11).

A Rice protein of 16 kDa has been shown to be involved in cross-allergenicity among antigens in Rice, Wheat, Maize, Japanese millet and Foxtail millet (4). However, Common millet was not assessed, and whether a similar protein can be found in this Millet is unknown.

Clinical Experience

IgE-mediated reactions

Hypersensitivity to cereals may occur via inhalation or ingestion. But in spite of Common millet being regarded as a potent allergen, allergy is uncommon, with reports generally confined to case studies (12).

With the increasing popularity of "natural foods", Millet is more frequently included in various dishes, which might raise the incidence of Millet-related allergic reactions. Patients with adverse effects to Gluten may substitute Millet for gluten-containing cereals.

Allergic reactions have been described after ingestion of Millet, and after inhalation of bird seed dust by people who keep caged birds (10,13). Case reports of asthma and/or anaphylaxis after ingestion of food containing Millet have been documented (7,8,10-11,14-17).

Individual cases are most instructive.

The first report of an adverse reaction to Common millet was described in a 25-year old clerk who developed anaphylaxis after the ingestion of Millet seed. Symptoms developed approximately 30 minutes after a "natural food" dinner, which included a Date-Millet pudding. The symptoms included periorbital angioedema, ocular injection, tightness of the throat, shortness of breath, wheezing, intense generalised pruritus, and lower abdominal distress. Significant intradermal skin-test reactivity to Millet extract was shown. IgE antibodies to Millet were elevated. Histamine release tests were positive. No cross-allergenicity between Millet seed and other grains and grasses (Rye, Orchard, and June grass pollen; Wheat, Oat, and Barley grain) was shown (8).

A meal containing Millet triggered an anaphylactic reaction in a young woman who kept a Parrot in a cage in her bedroom. Millet seeds were major constituents of the bird's feed (12).

A few minutes after ingestion of a cookie containing Millet, a 32-year-old woman developed laryngeal pruritus and oedema with stridor, tightness of the throat, pruritus of the palms and soles, conjunctivitis, facial swelling, and, a few minutes later, bronchospasm and hypotension. She had previously complained of laryngeal itching after ingestion of a pastry containing Millet, as well as of an episode of swelling of the

tongue in her childhood related to ingestion of a particular but unidentified cereal. No adverse effects were reported to other common cereals, including Barley and Wheat. Skin reactivity was determined for Barley seed and Wheat flour, but was negative for Barley flour, Maize seed and flour, and Oat seed and flour. Skin reactivity was present for fresh Millet seed extract. IgE antibody determination for Barley, Maize, Oats, and Wheat were negative but raised for Common millet (1.7, class 2). The authors highlighted the fact that, although skin reactivity was found for Wheat and Barley seed, she tolerated them well (7).

Anaphylaxis after ingestion of food containing Millet was reported in a 51-year-old woman who, after ingesting a Millet dumpling, immediately developed generalised urticaria, mucosal swelling, shortness of breath, and "hypotonic" reactions. She had not eaten Millet before. She had kept a Budgerigar years before and described having had asthmatic attacks while cleaning the bird cage. Skin reactivity was found only to Millet, which was strongly positive. Intradermal testing was positive for Rye, Oats, Maize, and Barley. SPT for Budgerigar allergens was negative. IgE antibody levels were raised for nearly all the cereals evaluated and in particular for Millet (9).

A study evaluated 7 individuals who all kept caged birds and had experienced allergic reactions after ingestion of Millet-containing food, with adverse reactions ranging from oral allergy syndrome to anaphylaxis. Symptoms included conjunctivitis (n=1), collapse (n=1), dyspnoea (n=3), hypotension (n=2), nausea (n=2), oral allergy syndrome (n=2), rhinitis (n=2), and urticaria (n=3). The individual profiles of these patients were the following: a 13-year-old male (nausea, hypotension), a 28-year-old female (oral allergy syndrome), a 32-year-old female (conjunctivitis, dyspnoea, urticaria), a 46-year-old female (rhinitis, dyspnoea, urticaria), a 62-year-old female (nausea, dyspnoea, urticaria, hypotension), a 30-year-old female (rhinitis), and a 40-year-old female (oral allergy syndrome). IgE antibody levels varied from ImmunoCAP classes of 2 to 4. As all of these subjects kept birds at home and used Millet as birdseed, the authors assumed that the sensitisation to Millet occurred via the inhalant route. Sixty-three percent of the bird keepers had IgE antibodies directed at Millet. Several patients reported respiratory symptoms while cleaning the bird cage. The authors suggested that sensitisation to Millet may subsequently also elicit food allergy (2).

Anaphylaxis was described in a bird-keeper sensitised to Millet via inhalation; the anaphylaxis occurred after oral ingestion (18).

Other reactions

Crude extracts of Millet may contain aflatoxins (19).

Some varieties of Millet appear to contain cyanide. (20) Fonio millet (Digitaria exilis) contains flavanoids with antithyroid properties and was reported to have resulted in an epidemic of severely iodine-depleted goiter, as a result of the presence of apigenin and of luteolin. Other Millets contain C-glycosylflavones (21). Millet diets rich in C-glycosylflavones are goitrogenic (22).

Jimson weed poisoning due to contamination of Millet porridge with this seed has been reported (23).

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f305 Fenugreek

Trigonella foenum-graecum

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Fenugreek, Greek Hay, Greek Fennel, Bird's Foot, Greek Hay-seed
Source material:	Dried seeds
Synonym:	*T. foenumgraecum*

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Allergen Exposure

Geographical distribution

Native to western Asia and south-eastern Europe, this aromatic legume plant is well known almost worldwide for its pleasantly bitter, slightly sweet seeds, sometimes described as having a suggestion of burnt sugar. Fenugreek grows today in many parts of the world, including India, northern Africa and the United States. The seed, dried for use, is about 3mm long, about 10 - 20 seeds being produced in each long pod. Its leaves are less widely in use. The seeds comprise of mucilaginous fibre (± 50% by weight) and steroid saponins (± 50% by weight) (1). It was primarily an animal fodder.

Environment

Fenugreek may grow wild, but for commercial purposes is generally cultivated. The very aromatic leaves (not generally available in the United States) can be used in salads, as a potherb or a flavoring, especially in curries. Pods may be cooked whole. Fenugreek seeds, which come whole and ground, are used to flavor many foods, including curry powders, spice blends and teas. The sprouted seeds can be added to salads or cooked. An essential oil obtained from the seed is used as food flavouring in imitation maple syrup, vanilla compositions, liquorice, pickles, etc. The roasted seed is a coffee substitute.

Fenugreek has many uses as an herbal medicine (both topical and ingested), especially in North Africa, the Middle East and India (2). Western pharmacological uses have borne out reports of the plant's efficacy. For example, Fenugreek and isolated Fenugreek fractions have been shown to act as hypoglycaemic and hypocholesterolaemic agents in both animal and human studies (1,3). Fenugreek has been purported to be effective in initiating and maintaining adequate milk production (4). Research has also shown that the seeds can inhibit cancer, lower blood cholesterol levels and have an antidiabetic effect. The seeds are very nourishing and are given to convalescents and to encourage weight gain, especially in anorexia nervosa. The seeds should not be prescribed medicinally for pregnant women, since they can induce uterine contractions.

Unexpected exposure

The plant is employed as a green manure crop, for cosmetic purposes, and as a dye ingredient.

Allergens

No allergens from this plant have yet been characterised, but allergens between 20 kDa to 70 kDa have been detected (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact is not seen frequently (5). In an *in vitro* study, the specific IgE binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked between the extracts of Peanut, Garden pea, Chick pea, and Soybean (6). However, clinical studies have found that there is little cross-reactivity between members of the legume family (7).

Clinical Experience

IgE-mediated reactions

Fenugreek has not commonly reported to induce symptoms of food allergy in sensitised individuals.

Reactions may follow ingestion, inhalation or external application of Fenugreek seed powder. Two cases of immediate severe allergy to Fenugreek have been described. In the first case, inhalation of the Fenugreek seed powder resulted in rhinorrhea, wheezing, and fainting. The second case was of a patient with chronic asthma who developed numbness of the head, facial angioedema, and wheezing after application of Fenugreek paste to her scalp as a treatment for dandruff. Skin reactivity was detected to Fenugreek and Chickpeas. During double-blind-placebo-controlled-food-challenge, both patients showed a > 20% drop in peak flow rate after consumption of Fenugreek and chickpea (2).

Anaphylaxis to curry powder was described in a 26-year-old nurse who presented with bronchospasm. Her initial symptoms were generalised itching, diarrhoea and stridor which were reproduced 20 minutes later following an oral challenge of curry and rice. The causative allergens were narrowed down to Cardamom and Fenugreek. Serum IgE antibodies to both were high (8).

An Algerian student using Fenugreek powder orally as an appetite stimulant and topically as a healing agent was reported to have rhinitis and asthma as a result of handling the powder. A prick test with Fenugreek powder was strongly positive (9).

Fenugreek has also been reported to result in occupational asthma (10).

This study describes a patient, working in a spice factory, with anaphylaxis from coriander in a meal. He also demonstrated urticaria, angioedema, rhinoconjunctivitis and bronchospasm during handling coriander and fenugreek. SPT, serum IgE antibodies and basophil activation tests were clearly positive in the patient. No cross-reactivity between fenugreek and coriander was demonstrable by inhibition experiments (11).

Other reactions

See also under Environment. The seed contains 1% saponins. Although poisonous, saponins are poorly absorbed by the human body and so most pass through without harm. Only large amounts tend to be dangerous. Leaching or thorough cooking will remove most saponins.

Non-steroidal anti-inflammatory drugs, particularly aspirin, have the potential to interact with herbal supplements containing coumarin, *e.g.*, Fenugreek, resulting in bleeding (12) or potentiation of the effects of warfarin therapy (13-14).

Fenugreek, maple syrup, and the urine of maple syrup urine disease patients all share a characteristic odour ("maple-syrup" urine odour), originating from a common component, sotolone (15-18). Maple syrup urine disease is an autosomal recessive inherited disorder of amino acid metabolism. The disease gives a characteristic sweet aroma, reminiscent of maple syrup, to the body fluids, *e.g.*, urine, of affected patients. The substance responsible for the odour is 4,5-dimethyl-3-hydroxy-2[5H]-furanone (sotolone), a compound also present in Fenugreek and Lovage (19). Ingestion of Fenugreek by mothers during labour resulted in a maple syrup-like odour in their newborn infants, leading to a false suspicion of maple syrup urine disease (15).

f305 Fenugreek

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Setaria italica

Family:	*Poaceae* (*Gramineae*)
Common names:	Foxtail millet, Italian millet, German millet, Hungarian millet, Siberian millet
Source material:	Peeled seeds
See also:	Common millet f55 and Japanese millet f57

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Allergen Exposure

Geographical distribution

The name Millet is used to describe seeds from several taxonomically divergent species of grass. They are grown mostly in marginal areas and under agricultural conditions in which major cereals fail to give sustainable yields (1).

See common background for Millets on page 60.

Foxtail millet and the other Millets are not closely related to Wheat.

Foxtail millet is used mainly in animal fodder and for bird seed. The main production area is China, but this is the most important Millet in Japan and is widely cultivated in India. Because of its fast maturation, it is a suitable crop for growing by nomads. The height of the plants varies from 1 to 1.5 m, and the colour of the grain varies from pale yellow through orange, red, brown and black (1).

Environment

See common background for Millets on page 60.

The Millets are important sources of food for humans and animals. But in the West, with the exception of natural food stores, Millet is sold mainly as bird feed.

Unexpected exposure

See common background for Millets on page 60.

Allergens

No allergens from this plant have yet been characterised.

A number of proteins have been isolated and described as occurring in Foxtail millet. The allergenic potential of these proteins was, however, not evaluated.

Barnyard millet, Common millet, Little millet, Foxtail millet and Kodo millet were studied. The protein contents of the selected decorticated Millets were found to be 11.0, 12.3, 12.9, 10.5 and 10.6%, respectively. Prolamin is a major storage protein in Foxtail millet, whereas glutelin is a major storage protein in all the other Millets. A protein band at the molecular weight range of 20 kDa was found to be homologous in all except Proso millet (2).

A Foxtail millet glutelin of 60 kDa (MG60) has been isolated. The primary structure at the N-terminal end was almost identical to those of the granule-bound

starch synthase (GBSS) proteins from Rice, Barley, Maize, Wheat and Potato. Common epitopes from these starch-storing cereals were corroborated by immunoblot analysis, strongly suggesting a close relationship (3).

In a study, the antigenic relationships among "minor Millets" (Barnyard, Little and Foxtail millets) and other cereals (Wheat, Maize, Rice, Sorghum, Finger millet and Pearl millet) were evaluated using an antibody raised against a 20 kDa prolamin from Kodo millet. It was demonstrated that the prolamin was related to the prolamins from the other plants. Rice was the only common cereal that did not cross-react immunologically with the 20 kDa prolamin of Kodo millet (4).

A subtilisin inhibitor has been isolated from seeds of Foxtail millet (5).

Proteinase inhibitors (trypsin/chymotrypsin) have been demonstrated to be present in Finger millet, Sorghum, Pearl millet, Foxtail millet, and Japanese millet (6). The amino acid sequence of an isolated trypsin inhibitor (7) had a high degree of homology to Bowman-Birk type inhibitors from leguminous and gramineous plants (8).

Cross-allergenicity among Rice, Wheat, Maize, Japanese and Foxtail millet was examined by IgE antibody determination and RAST inhibition studies, demonstrating significant close correlations among the 5 cereal grain extracts. A Rice protein of16 KDa was shown to be one of major allergens in Rice grain extracts (9-10). The protein showed sequence homology to Wheat alpha-amylase inhibitor and Barley trypsin inhibitor (11). The clinical relevance of this protein was not assessed.

Potential cross-reactivity

A Rice protein of 16 kDa has been shown to be involved in cross-allergenicity among antigens in Rice, Wheat, Maize, Japanese millet and Foxtail millet (10). The clinical relevance of this allergen was not examined.

In a study, the antigenic relationships among "minor Millets" (Barnyard, Little and Foxtail millets) and other cereals (Wheat, Maize, Rice, Sorghum, Finger millet and Pearl millet) were evaluated using an antibody raised against a 20 kDa prolamin from Kodo millet. It was demonstrated that the prolamin was related to the prolamins from the other plants. Rice was the only common cereal that did not cross-react immunologically with the 20 kDa prolamin of Kodo millet (4). The clinical significance of this was not evaluated.

Clinical Experience

IgE-mediated reactions

Hypersensitivity to cereals may occur via inhalation or ingestion, but reported allergy to Foxtail millet is rare.

With the increasing popularity of "natural foods", Millet is more frequently included in various dishes, which might raise the incidence of Millet-related allergic reactions. Patients with adverse reaction to Gluten may substitute Millet for gluten-containing cereals.

Little information is available on the allergens causing symptoms in patients with atopic dermatitis. One study analysed the IgE immune response to various cereals and to specific protein fractions of Wheat and Oats in children with severe atopic dermatitis (AD) and correlated the results with challenge studies. In SPT studies, 33 children were positive for Wheat and 18 for Oats. SPT for Rice, Maize, Millet or Buckwheat were positive in 16 of the 34 patients (12).

IgE antibodies against Foxtail millet were found in serum of patients with atopic dermatitis with or without bronchial asthma (9).

Other reactions

Crude extracts of Millet may contain aflatoxins (13).

Millet diets rich in C-glycosylflavones are goitrogenic (14).

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f79 Gluten

Common names:	Gluten, Tri a Gluten, Gliadin, Gamma-Gliadin, Omega-gliadin
Source material:	Gluten from Wheat
See also:	Wheat f4, Barley f6, Rye f5, Oat f7, rTri a 19; Omega-5 Gliadin f416

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Allergen Exposure

Geographical distribution

Gluten is the elastic rubbery protein present in Wheat, Rye, Barley and to a lesser degree in Oats. It binds the dough in bread and other baked goods. It contributes to consistency and sponginess.

Only Gluten from Wheat (and close family members), Barley, Rye and Oats may result in symptoms of coeliac disease (CD) in susceptible individuals. Although Oats contains Gluten, studies have reported that levels are too low to warrant exclusion by individuals with CD. In contrast, Wheat starch with a 0.3% protein level has an actual Gluten content of around 200 ppm (mg/Kg).

Environment

Food derived from Wheat, Barley and Rye contains gliadin and is toxic to individuals with CD. Because the type and proportion of prolamin proteins in grains vary, the kind of reaction (if any) they are likely to cause also varies. Corn, Rice, other cereal grains such as sorghum, millet, teff, ragi and Job's tears as well as Buckwheat, quinoa and amaranth can safely be ingested by a person with CD. Wheat, Rye, Barley, Spelt and kamut, however, should be avoided in CD. Although Oats contain Gluten, studies have reported that levels are too low to warrant exclusion by individuals with CD. However, there are concerns among some authorities on coeliac disease that even if Oats themselves are safe, they nonetheless may be contaminated with Wheat, Rye, or Barley (1).

Unexpected exposure

Some foods contain gliadin because they are direct derivatives from Wheat, such as glucose and maltose syrups. Also posing dangers are Wheat germ oil, and alcoholic beverages obtained from various gliadin-containing grains, such as beer made from Barley. In other foods, the residual Wheat proteins may derive from production practices; blue cheeses or mold-covered cheeses, for example, should not be allowed in a Gluten-free diet, since *Penicillium inocula* are grown on bread, and therefore are thought to contain residual gliadin (2).

Allergens

The Gluten allergen has been identified and characterized:

The gliadin and glutenin proteins form a "complex" and have been termed Gluten; *i.e.*, Gluten is composed of gliadin and glutelin. Wheat flour contains between 7% and 12% Gluten proteins by weight. Gluten is also known as Tri a Gluten, Gliadin, Gamma-gliadin and Omega-gliadin. See Wheat f4 for details on the individual gliadins (*e.g.*, Tri a alphabeta-gliadin, Tri a alpha-gliadin, Tri a beta-gliadin, Tri a omega-2 gliadin), and glutelin.

Gluten consists mainly of proteins (~ 90%), which can be divided into alcohol-soluble gliadins and alcohol-insoluble glutenins. Wheat flour contains between 7% and 12% Gluten proteins by weight. All gluten proteins are high in proline and glutamine contents, and that is the predominant basis for calling them prolamins. Cereal prolamins have no known function apart from storage and are the major storage proteins in most cereal seeds (3-4). Prolamins consist of a heterogeneous mixture of proteins of a molecular weight 30-90 kDa (5). There are specific names for individual prolamins from different species: secalins from Rye, hordeins from Barley, zeins from Maize, and avenins from Oats.

The following is a list of the type of prolamin in each grain and the percentage that the prolamin contributes to the grain's protein content:

Wheat:	Gliadin	69%
Corn:	Zein	55%
Barley:	Hordein	46-52%
Sorghum:	Kafirin	52%
Rye:	Secalinin	30-50%
Millet:	Panicin	40%
Oats:	Avenin	16%
Rice:	Orzenin	5%

The 70% ethanol-soluble gliadins of a single Wheat grain can be separated into up to 50 components and are a heterogeneous mixture of single-chained polypeptides. They are divided into 4 groups, here in descending order of mobility in accordance with acid-PAGE studies: alpha-, beta-, gamma-, and omega-gliadins (6). Their molecular weight ranges from around 30 to 75 kDa.

The 70% ethanol-insoluble glutenins are divided into high-molecular-weight (HMW) and low-molecular-weight (LMW) glutenins.

The major difference between glutenins and gliadins is in their functionality. While gliadins are single polypeptide chains (monomeric proteins), the glutenins are multichained structures of polypeptides that are held together by disulfide bonds.

Data suggest that the different prolamins may share regions of amino acid sequence homology with each other and with some of the water/salt soluble albumin/globulin proteins (7).

Another classification of the gluten proteins is based on the amino acid sequences and does not correspond precisely to the gliadin/glutenin classification for Wheat prolamins discussed above, which is based on the ability of the proteins to form inter-molecular disulphide bonds. In contrast, this further classification divides the proteins into 3 groups: sulphur-poor (S-poor), S-rich, and high-molecular-weight (HMW) prolamins.

The S-poor prolamins comprise the omega-gliadins of Wheat, the omega-secalins of Rye, and C hordeins of Barley. The S-rich prolamins are the major group of prolamins present in Wheat, Barley and Rye, accounting for approximately 80% of the total fractions. They comprise the alpha-gliadins, the gamma-gliadins and LMW glutenin subunits of Wheat, the gamma and B hordeins of Barley and the 40 kDa and 75 kDa gamma-secalins of Rye. The HMW subunits of Wheat glutenin play an important role in determining the breadmaking quality of Wheat. HMW prolamins are also present in Barley and Rye, where they are called D hordein and HMW secalins, respectively.

Early studies demonstrated that a number of Wheat allergens play diverse roles in allergy to Wheat (8-14). Although the albumin and globulin fractions are the most prevalent allergens in Wheat-allergic individuals, IgE binding has been demonstrated to the water/salt-insoluble fractions (gliadin and glutenin) of Wheat flour (5,15).

The alpha- and fast omega- are the most immuno-reactive gliadins, with the total glutenins also being highly immuno-reactive. The development of IgE antibodies to alpha-gliadin and total glutenins is to a moderate degree associated with the development of IgE antibodies to water/salt-soluble Wheat allergens and may be due to the presence of cross-reacting epitopes in the prolamins and the water/salt-soluble albumins/globulins, in particular enzyme inhibitors. The development of allergen-specific IgE to the majority of gliadins is independent of both the levels of total IgE and the development of IgE antibodies to water/salt-soluble proteins, suggesting that 2 or more populations of IgE may be involved in hypersensitivity to cereal

prolamins: those which bind to epitopes homologous to those found in water/salt-soluble proteins, and those which bind to the -rich repetitive domains of prolamins (16).

Similarly, in a study assessing the allergenicity of the protein fractions extracted from Wheat flour with indicated solvents, the gliadins (ethanol) were the strongest allergens, followed by glutenins (acetic acid), albumins (water), and globulins (salt water). Of the gliadins, the alpha and beta fractions were most potent, followed by the gamma and omega types (17).

LMW glutenin, alpha-gliadin, and gamma-gliadin have been identified as allergens in Wheat-allergic patients (18). Alpha-gliadin and fast omega-gliadin have been reported to be the allergens associated with baker's asthma (5). Low-molecular-weight (LMW) glutenin, one of the water/salt-insoluble proteins, has been reported to be the major allergen for patients allergic to Wheat (19-20). Other researchers have shown that alpha-gliadin and -gamma-gliadin, in addition to LMW glutenin, are the allergens for patients with Wheat allergies (18).

Although glutenins usually occur in Wheat as polymers with molecular weights of up to 1000 kDa and are held together by disulphide bonds, low-molecular-weight glutenin subunits have been identified (4-16).

Individual types of gliadin found in Gluten have been characterised and may each individually or in various combinations result in sensitisation. For example, omega-5 gliadin (Tri a 19) from Wheat, a gliadin, also known as fast omega-gliadin, has been reported to be a major allergen in WDEIA (14,18,20-32). Approximately between 66% and 92% of Wheat-allergic patients are positive to this allergen. In a study to determine IgE binding against a panel of purified Gluten proteins by using sera from 15 patients with WDEIA, approximately 80% of the patients reacted to fast omega-gliadin, strongly confirming that this allergen is a predominant allergen for WDEIA (14). Further information on omega-5 gliadin will be found at Wheat f4 in this reference book, and recombinant omega-5 gliadin at rTri a 19; Omega-5 Gliadin f416 (Separate reference book).

Potential cross-Reactivity

Studies of Wheat allergens have reported various degrees of cross-reactivity. Wheat water/salt-soluble proteins were reported to cross-react with alpha-gliadin and total glutenins, the water/salt-soluble proteins sharing cross-reacting epitopes with water/salt-insoluble proteins. The authors suggested that the development of IgE antibodies to alpha-gliadin may in part depend on the presence of cross-reacting antibodies to water/salt-soluble Wheat allergens (5). Clear cross-reactivity was also reported between gliadin and other fractions; the authors concluded that identical epitopes are found in several different allergenic molecules of the cereal flours despite their different solubility (5).

Fast omega-gliadin is a major allergen among water/salt-insoluble proteins in the case of Wheat-dependent exercise-induced anaphylaxis in Japanese patients, and IgE against fast omega-gliadin cross-reacts to gamma-gliadin and slow omega-gliadin (32). Further studies have reported that gamma-70 and gamma-35 secalins in Rye and gamma-3 hordein in Barley cross-react with omega-5 gliadin, suggesting that Rye and Barley may elicit symptoms in patients with Wheat-dependent exercise-induced anaphylaxis. In immunoblotting, anti-omega-5 gliadin antibodies bound to 70 kDa and 32 kDa proteins in Rye and to a 34-kDa protein in Barley, but not to proteins in Oats. These proteins were identified as Rye gamma-70 secalin, Rye gamma-35 secalin and Barley gamma-3 hordein, respectively. In ELISA studies, 21/23 (91%) patients with Wheat-dependent exercise-induced anaphylaxis showed IgE antibodies to purified gamma-70 secalin, 19/23 (83%) to gamma-35 secalin and 21/23 (91%) to gamma-3 hordein. Skin prick testing gave positive reactions to gamma-70 secalin in 10/15 (67%) patients, to gamma-35 secalin in 3/15 (20%) patients and to gamma-3 hordein in 7/15 (47%) patients (24).

Although extensive cross-reactivity can be expected among the varieties of Wheat, Einkorn Wheats, particularly *T. monococcum*, are suspected to be less toxic than bread and pasta Wheats to patients with coeliac disease (33).

Clinical Experience

IgE-mediated reactions

Gluten is among the most important food components accounting for hypersensitivity reactions in children. Adverse reactions to Gluten protein include:

1. Food allergy,
2. Food-dependant exercise-induced asthma or anaphylaxis,
3. Coeliac disease, a non-IgE-mediated enteropathy caused by gliadin.

The onset of adverse reactions in the first 2 conditions may be immediate, delayed, or both immediate and delayed (34).

Sensitisation and allergic reactions to distinct gliadins and glutelin are discussed in detail at Wheat f4.

Overview of food allergy to Gluten

The majority of IgE-mediated reactions to Wheat involve the albumin and globulin fractions. Gliadin and Gluten in Wheat, Barley and Rye may also induce IgE-mediated reactions. There is increasing evidence that components of gliadin are involved in baker's asthma. See Wheat f4, Barley f6 and Rye f5 for further information.

Sensitisation to Gluten by ingestion can lead to food allergy symptoms, whereas sensitisation by inhalation causes baker's asthma and rhinitis. For example, Wheat omega-5 gliadin (Tri a 19) has been shown to be a major allergen in children with immediate allergy to ingested Wheat (21).

Gluten-dependent exercise-induced anaphylaxis

The major allergen resulting in Gluten-dependant exercise-induced anaphylaxis (GDEIA) is a gliadin, a common and cross-reactive allergen found in Wheat, Barley and Rye. The condition is more commonly defined according to the predominant food involved, *i.e.*, Wheat-, or Barley-, or Rye-dependant exercise-induced anaphylaxis. GDEIA is a severe IgE-mediated allergic reaction provoked by the combination of the ingestion of food containing Gluten with intensive physical exercise during the next few hours (26,28-30,35-39). Typical symptoms are generalised urticaria and severe allergic reactions such a shock or hypotension (14). GDEIA may occur to multiple food intake (40).

The involvement of Gluten in this condition has been suggested from studies of Wheat. Of the Wheat proteins, omega-5 gliadin (Tri a 19), one of the components of fast omega-gliadin, has been reported to be a major allergen in WDEIA (18). Although the mechanism is not fully understood, a study reports that omega-5 gliadin-derived peptides are cross-linked by tissue transglutaminase (tTG), which causes a marked increase in IgE binding both *in vitro* and *in vivo*. Activation of tTG, during exercise, in the intestinal mucosa of patients with WDEIA could lead to the formation of large allergen complexes capable of eliciting anaphylactic reactions (23). A study suggests that, in addition to IgE antibodies against omega-5 gliadin, IgA antibodies may be involved in the pathogenesis of WDEIA (27).

See Wheat f4 for more on this condition.

Atopic Dermatitis

Wheat, and in particular the Gluten component, may result in or exacerbate atopic dermatitis (AD) (41-42). The strong association between positive oral Wheat challenge and positive SPT with ethanol-soluble gliadin suggests that gliadin is an important allergen for Wheat-allergic children with AD (43).

SPT with a NaCl Wheat suspension and ethanol-soluble Wheat gliadin was performed on 18 Wheat challenge-positive or Wheat challenge-negative children with AD, 6 adult AD patients with suspected cereal allergy, and 1 adult with Wheat-dependent exercise-induced urticaria/anaphylaxis. It was reported that 13 of the AD children were Wheat-challenge-positive, that 11 were SPT positive for gliadin and that all had elevated Gluten-specific IgE levels. Those who were challenge-negative were negative with both SPT to gliadin and Gluten-specific IgE test. Four of the adult patients responded to a cereal-free diet, although only 2 of them appeared to be positive with gliadin SPT and Gluten-specific IgE test (43).

Other IgE-mediated food reactions

Gluten may be a "hidden allergen" (44).

Baker's asthma

Baker's asthma is a frequent allergy in the baking industry. In Germany, approximately 1,800 bakers annually claim compensation for baker's asthma (45). The prevalence of asthma among bakers has been shown to be around 10%, and the prevalence of cereal allergy 15-25% (46-47). Of those bakers who have cereal allergy, up to 35% experience asthma (48). In Japan in recent years, the number of patients suffering from baker's asthma caused by bread Wheat has been increasing, and includes not only people engaged in food industries, but also those who live near a factory producing Wheat flour products (49).

Several protein components of salt extracts of Wheat flour weighing from 10 to 100 kDa have been identified as major IgE-binding proteins in occupational asthma (50). IgE antibodies to a number of flour components have been demonstrated in allergic bakers' sera, with the strongest reactivities occurring to water-soluble Wheat albumins and globulins, with the former shown in inhibition studies to be more reactive than the latter (51-53). However, further analyses have demonstrated that major IgE-binding proteins are found in other fractions (gliadin and glutenin) as well (53).

Other reactions

Non-IgE immune reactions to Gluten may result in coeliac disease.

Coeliac disease is widespread, occurring in 0.5-1% of the population. Coeliac disease is traditionally associated with European countries, particularly Scandinavia, but is now commonly seen in populations of European ancestry (North and South Americas, Australia), and in North Africa, the Middle East and South Asia (54). In adults, the prevalence appears to be 1 in 250-300, while in children it may be as high as 1 in 100 (54-55). The prevalence of coeliac disease among school children from India is not rare in Wheat-eating areas of North India (56).

CD disease may occur at any age. In infants, symptoms will usually appear only a few months after the introduction of foods containing Gluten into the diet (6-12 months); in adulthood, the onset is usually between 30-40 years (57). After onset, it is a life-long disorder. It tends to affect twice as many females as males.

CD is thought to be the result from an inappropriate T-cell-mediated immune response against ingested Gluten in genetically pre-disposed individuals. It is caused by IgA- and IgG-mediated immune responses, and approximately 90-95% of cases are linked to the HLA-DQ2 gene complex, while 5-10% are seen in those with HLA DQ8 gene complexes. Sensitisation and activation of the T-lymphocytes lead to inflammation and structural alteration of the mucosal lining. The enzyme tissue transglutaminase is one of the targets of the autoimmune response in coeliac sprue. The enzyme converts particular glutamine residues in Gluten peptides into glutamic acid, which results in a higher affinity of these peptides for HLA-DQ2 or HLA-DQ8 (negative charges are preferred at anchor positions in the peptide-binding groove of this molecule) (54,58-62).

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Phaseolus vulgaris

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Green bean, Common bean, French bean, String bean, Snap bean, Wax bean, Haricot bean
Source material:	Fresh beans
See also:	White bean f15 and Red kidney bean f287

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Allergen Exposure

Geographical distribution

The genus *Phaseolus* includes many varieties of edible Beans. The Green bean, also known as the French bean or Common bean, has a long, slender green pod with small seeds inside. The entire pod is edible. The Wax bean is a pale yellow variety of Green bean.

The pods are usually harvested when immature, before the seeds inside have grown too large. When the pods are left on the plant to mature fully, the ripe seeds can then be dried and used as Haricot beans.

Environment

The green pods are commonly used as a vegetable. The young leaves can be eaten raw or cooked as a potherb.

The green or dried mature pods, or the seeds alone, are diuretic, hypoglycaemic and hypotensive. Ground into flour, the seeds are used as a homeopathic remedy.

Allergens

No allergens from this plant have yet been fully characterised.

A 32 kDa IgE-binding protein, a class I chitinase closely resembling the major Avocado allergen Prs a 1, has been isolated. This reactive component was strongly induced by ethylene treatment. Immunoblot inhibition assays demonstrated cross-reactivity between the 2 allergens. The purified allergen, designated PvChI, induced positive skin prick test responses in 7 of 8 patients with Latex-fruit allergy. This allergen was completely inactivated by heating (1).

Green bean probably contains heat-labile and heat-stable allergens. A 35 kDa protein, probably a novel allergen and not a chitinase, was detected in a 20-year-old girl who experienced anaphylaxis to Green bean. She reacted to boiled Green bean, which induced a stronger reaction than raw Green bean (2). That some allergens are differently sensitive to heat was demonstrated in a second study, in which boiling completely abolished skin reactivity (3). In 3 women who developed asthma and rhinitis after exposure to raw Green beans, but who tolerated ingestion of cooked Green beans, immunoblots of raw and cooked Green bean extract showed 2 IgE-binding bands with apparent molecular weights of 41.1 and 70.6 kDa. A 47 kDa IgE-binding protein was detected only in raw Green bean extracts (4).

A common feature of most legume allergens is their natural resistance to thermal, chemical, and, in some respects, proteolytic denaturation (5).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact does not occur frequently (6). In an *in vitro* study, the specific IgE binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be frequent, and most marked between the extracts of Peanut, Garden pea, Chick pea, and Soybean (7). However, clinical studies have found that there is little cross-reactivity between members of the legume family (8-10).

Nevertheless, legumes are an important ingredient in the Mediterranean diet, and among Spanish children, sensitivity to legumes is the fifth most prevalent food allergy. Lentil and Chick pea are the most frequent causes of allergic reactions to legumes in Spanish children. A high degree of cross-reactivity has been demonstrated among Lentil, Chick pea, Pea and Peanut. Unlike in other populations, in Spanish children this phenomenon implies clinical sensitisation for many. In a study of 39 Spanish children challenged (open or simple blind) with 2 or more legumes, 82% reacted to 2 or more legumes: 43,5% to 3, 25,6% to 2, and 13% to 4 legumes. However, and surprisingly, the legumes White bean and Green bean and Soy were well tolerated by children allergic to other legumes. Therefore the diagnosis of legume allergy should not be based only on allergen specific IgE tests (11).

PvChI, a class I chitinase closely resembling the major Avocado allergen Prs a 1, was demonstrated through immunoblot inhibition assays to be cross-reactive (1).

A study investigated the *in vitro* cross-reactivity of allergens from Mesquite tree pollen (Honey Locust tree; *Prosopis juliflora*) and Lima bean (*Phaseolus limensis*/ *Phaseolus lunatus*). Of 110 patients with asthma, rhinitis or both, as evaluated with intradermal skin test, 20 were highly positive to Mesquite pollen extract. Of these, 12 patients showed elevated IgE antibody levels to Mesquite pollen extract alone, and 4 to both Lima bean and pollen extract. Lima bean extract could inhibit IgE binding to Mesquite in a dose-dependent manner. Also, humoral and cellular cross-reactivity was demonstrated (12). Although cross-reactivity was not investigated between Mesquite and Green bean *per se*, cross-reactivity may exist between pollen from this tree and other species of *Phaseolus*.

Clinical Experience

IgE-mediated reactions

As a member of the legume family, the Green bean may often result in symptoms of food allergy. Allergic reactions caused by skin contact or by inhalation of vapor from raw or boiling Green bean have also been reported (3-4).

Asthma and rhinitis were reported in 3 women after exposure to raw Green bean (and 1 also when exposed to raw Chard). All women tolerated ingestion of cooked Green beans. Multiple episodes while handling these vegetables for cooking were reported. SPT and serum IgE antibody test were positive. Bronchial challenge tests with these allergens showed positive responses to raw but not cooked Green bean and Chard. Oral food challenges with Green bean (raw and cooked) and Chard were negative in all patients (4). Similar symptoms were reported in a homemaker, who experienced rhino-conjunctivitis, occupational asthma, and contact urticaria while trimming raw Green beans or inhaling vapour from boiling Green beans. She was able to eat and touch cooked Green beans without any ill effect and showed no reactivity to any other foods. Skin reactivity was detected to an allergen in raw Green beans, but not to boiled Green beans. Rubbing the raw Green bean on the patient's forearm elicited wheals and pruritus within 10 minutes. Bronchial provocation test with both Green bean extracts was positive and immediate. Basophil histamine release test was positive (3).

In an atopic housewife, rhino-conjunctivitis and acute asthma associated with unrelated family members, Green bean and Swiss Chard, have been reported. Skin tests, histamine release test, IgE antibody determination, and bronchial responses after

specific bronchial challenges were positive for both (13).

Reactions may be severe. Anaphylaxis was described in a 20-year-old girl, which occurred 1 hour after ingestion of Green beans. Her symptoms included gastroenteritis, generalised urticaria and collapse. SPT demonstrated a greater positivity to boiled Green bean, inducing a stronger reaction than raw Green bean (2).

A 7-year-old boy developed angioedema associated with inhalation of vapour from cooked White bean. SPT evaluated using a prick-by-prick method with White bean was positive. IgE antibody levels was raised for White bean and a closely related family member, Green bean. The patient developed angioedema after ingestion of cooked White bean (14).

Recurrent otitis media with effusion was reported to be associated with a variety of foods, including beans, but not specifically Green bean. Due to the close family relationship between these legumes, Green bean may in future be shown to be similarly responsible (15).

Other reactions

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe cell-mediated gastrointestinal food hypersensitivity typically provoked by Cow's milk or Soy. A study reported on other foods causing this syndrome: 14 infants with FPIES caused by grains (Rice, Oat, and Barley), vegetables (Sweet potato, Squash, String beans, Pea), or poultry (Chicken and Turkey) were identified. Typical symptoms of FPIES are delayed (median: 2 hours) and include vomiting, diarrhoea, and lethargy/dehydration. Eleven infants (78%) reacted to >1 food protein, including 7 (50%) who reacted to >1 grain. Nine (64%) of all patients with solid food FPIES also had Cow's milk and/or Soy FPIES. Initial presentation was severe in 79% of the patients, prompting sepsis evaluations (57%) and hospitalisation (64%) for dehydration or shock. None of the patients developed FPIES to maternally ingested foods while breastfeeding unless the causal food was fed directly to the infant (16).

Occupational contact dermatitis caused by the leaves of *Phaseolus* plants has been reported in a farmer (17).

f315 Green bean

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Corylus avellana

Family: *Betulaceae* (*Corylaceae*)

Common names: Hazel nut, Hazelnut, Filbert, Cobnut, Cob

Source material: Shelled nuts

The terms "Filbert" and "Hazel nut" are often used interchangeably for nuts from all plants in the genus *Corylus*, such as *C. silvestris*, *C. maxima* and *C. colurna*

See also: Hazel t4

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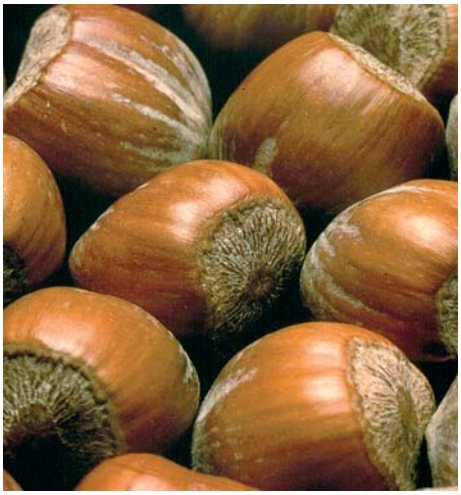

Allergen Exposure

Geographical distribution

These wild nuts grow in clusters on the Hazel tree in temperate zones around the world. Hazel is an aggressive spreader and is particularly common in Europe as a wild growth, where it has played a significant role in the development of the present forest ecology. Archaeology shows that the nuts were a prehistoric food and the wood a building material, and that tree populations were not adversely affected by land clearance for Neolithic farming.

The tree grows up to 8 m and has a smooth, copper-coloured bark, which peals off in thin papery strips; and twigs covered in thick, reddish, glandular hairs. The fertilised flowers develop into clusters of nuts. The fruit, a 2 cm nut, is surrounded by a leafy bract and ripens in late summer. The fuzzy outer husk opens as the nut ripens, revealing a hard, smooth shell, inside of which is a sweet, rich, grape-size nut within a bitter brown skin that is sometimes removed. Italy, Spain, France and Turkey lead in Hazel nut production. The nuts generally fall in the autumn and are harvested from the ground and then shelled and dried.

Environment

Many Hazel trees grow wild, aggressively forming coppices and scrub. Particularly when cultivated, the nuts (often under the name "Filberts") are used chopped, ground, roasted, blanched, sliced, and as flour and paste in all manner of sweets. They are also eaten whole as a snack (often among "mixed nuts"). During the Western holiday season, bowls of mixed nuts still in their shells are traditionally served, to be cracked with nutcrackers; Hazel nuts are prominent in these mixtures. Hazel nuts also add flavour and texture to savoury items such as salads and main dishes.

Unexpected exposure

Hazel nut is widely used and can be a "hidden" allergen; for example, nougat, an ingredient in secondary products such as confections, is a Hazel nut product.

Allergens

Various allergens have been isolated and characterised in Hazel nut:

Cor a 1, a 18 kDa protein, a Bet v 1 homologue and a major Hazel nut allergen (1- 2).

Cor a 1.04, and variants (3-4).

Cor a 2, a 14 kDa protein, a profilin (5).

Cor a 8, a 9,4 kDa protein, a lipid transfer protein (2-3,6-7).

Cor a 9, a 40 kDa, 11S globulin-like protein, a major protein (8).

Cor a 11, a 7S vicilin-like globulin

Cor a Oleosin (9).

Cor a Heat Shock Protein (10).

The Hazel nut major allergens identified to date are an 18 kDa protein homologous to Bet v 1 and a 14 kDa allergen homologous to Bet v 2. A 47, a 32, and a 35 kDa allergen were detected and reported to be major allergens. The 18 kDa protein was abolished in roasted Hazel nut. The 47 kDa allergen was shown to be a sucrose-binding protein, the 35 kDa allergen a legumin, and the 32 kDa allergen a 2S albumin. Patients with severe anaphylactic reactions to Hazelnut showed IgE reactivity to a 9 kDa allergen that was characterised as a heat-stable lipid transfer protein (LTP) (6,11). The Bet v 1 homologue allergen may have been the allergen now identified as Cor a 1. Roasting of the nuts appears to significantly reduce allergenic activity. Binding of Cor a 1 was severely decreased after heating to 80 °C and higher. No activity of this allergen could be detected in roasted Hazel nut meal.

Three isoforms have been described in Hazel tree pollen, Cor a 1.01, 1.02, and 1.03; and 1, Cor a 1.04, in Hazel nut. Cor a 1.04 shares greater identity with the Birch pollen allergen Bet v 1 (85%) than with its own pollen homologue. A comparison of Birch and Hazel tree pollen extracts and Hazel nut Cor a 1.04 suggests that in some populations, the majority of patients are primarily sensitised by Birch Bet v 1 (13).

Cor a 1 isoforms of Hazel nut display different antigenic and allergenic properties, very likely due to few but significant variations in their amino acid sequences (12). Cor a 1 isoforms appear to represent a complex set of gene products, some of which are more allergenic than others. Cor a 1.04 is a 17.4 kDa protein expressed in at least 4 sub-isoforms, Cor a 1.0401-1.0404, which are 97-99% identical to each other but share only 63% and 71% identity with the Hazel pollen isoforms Cor a 1.0101 and Cor a 1.0301, respectively. Despite the high degree of identity between the 4 nut isoforms, and despite the fact that between 91% and 95% of 43 Hazel nut-allergic patients were reactive with 3 of the 4 versions, 1 form, Cor a 1.0404, reacted with only 74% of the patients (4).

Sensitisation to Cor a 1.04 was demonstrated in 16/17 patients, and to Cor a 2 in 7/17 patients. None of this particular group of patients appeared to be sensitised to the lipid transfer protein Cor a 8 (3). This may indicate that Cor a 8 is a minor allergen in some populations, but a major allergen in others (see below).

Cor a 1.04 has been identified as the major Hazel nut allergen in 65 European patients with positive double-blind, placebo-controlled food challenges to Hazel nut. The 11S globulin Cor a 9 was shown to be a pollen-independent Hazel nut allergen in the United States, whereas the indications were that Cor a 8, a lipid transfer protein (LTP), was an important Birch pollen-unrelated Hazel nut allergen in Europe. Twenty-six Spanish patients allergic to Hazel nut without Birch pollen allergy, including 10 patients with anaphylaxis, were evaluated for sensitisation to Cor a 8. The prevalence of IgE antibody reactivity to this LTP (Cor a 8) was 62% in Hazelnut extract, and 77% to the recombinant LTP. Natural Cor a 8 and rCor a 8 shared identical epitopes. Only 1 patient had positive reactivity to Cor a 1.04, and no patients had positive reactivity to Cor a 2. Two sera bound to high-molecular-weight allergens. Cor a 8 was therefore shown to be a major allergen for a majority of Spanish patients with Hazel nut allergy, and was responsible for severe allergic reactions (2).

Cor a 9 was recognised by IgE antibodies from 86% (12/14) of patients with Hazel nut allergy and systemic reactions (8).

A low-molecular-weight (17 kDa) heat shock protein recognised by IgE from 10 of 14 (71%) Hazel nut-allergic patients is described (10,13).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (14). Cross-reactivity between Hazel nut and Hazel tree pollen may occur. IgE antibodies from all 25 patients displaying type I allergic reactions to the tree pollen as well as allergy to Hazel nuts bound to the major Hazel pollen allergen Cor a 1; and in 16% of the patients the IgE antibodies bound to the 14 kDa Hazel tree pollen profilin. IgE binding to proteins of comparable molecular weights in Hazel nut extracts (18 kDa and 14 kDa) was found, suggesting that proteins similar to Cor a 1 and Hazel profilin might also be expressed in Hazel nuts (5,15).

Indeed, where trees of the family *Betulaceae* (*e.g.*, Birch, Alder, Hazel and Hornbeam) are prevalent, the cross-reactivity between sensitising pollen and nut allergens can be the leading cause of food allergies (13). Other authors have found a relationship between Birch pollinosis and sensitisation to Hazelnut, Apple, Kiwi, Carrot, Potato and other vegetables (16-17).

Of 196 Birch pollen-hypersensitive patients with Oral Allergy Syndrome, 195 had Apple and/or Hazel nut allergy, and 103 were sensitised to food from the *Apiaceae* family, suggesting that most *Apiaceae* allergens cross-react with Apple or Hazel nut allergens, whereas only some Apple or Hazel nut allergens cross-react with *Apiaceae* allergenic proteins (18).

A 80.5-83% similarity was demonstrated between Cor a 1 isoforms and Bet v 1, the major Birch pollen allergen (12). Allergy to Hazel nuts can therefore be regarded as a common example of Birch pollen-related food allergy (3). Binding to Bet v 1 was abolished in roasted Hazel nut (6).

A similarity of 83.6-85% appears to exist between Cor a 1 isoforms and published sequences of Aln g 1, the major allergen from Alder tree; and a 89.3-95% similarity between Car b 1 (and isoforms), the major allergen from Hornbeam tree. IgE antibodies from tree-pollen-allergic patients reacted with all 4 recombinant isoforms. However, marked differences in the IgE binding patterns of the distinct isoforms were noted (12).

The presence of a Bet v 1-like allergen may explain the association of Hazel nut allergy with other allergies. In individuals with Kiwi allergy, strong reactions to Apple and Hazel nut were reported and moderate reactions to Carrot, Potato and Avocado. RAST inhibition studies revealed cross-reacting antigens between Birch pollen and Kiwi fruit (19).

A 45 and a 30 kDa protein were isolated and shown to have a 60% homology to the conglutin gamma heavy chain from Lupin seed and to a 7S globulin from Soybean, respectively. A 12 kDa protein, probably a 2S albumin, displayed a high degree of homology to the 2S albumin from English walnut (Jug r 1). Immunoblot inhibition and IgE binding to Almond 2S albumin and conglutin gamma were demonstrated in the presence of cross-reacting Walnut or Hazel nut antigens (20).

An important cross-reactivity among the pollen of *Platanus acerifolia* (London plane tree), Hazel nut and Banana has been reported (21).

Birch may not be the only source of pollen-induced cross-reactivity, as Mugwort (*Artemisia vulgaris*) pollen has also been shown to be cross-reactive with Hazelnut allergens and may also be a sensitising agent. In a pool of 28 individual sera with IgE antibodies to Mugwort pollen and Hazel nut, IgE antibodies to Hazel nut was inhibited up to 63% by Mugwort pollen. However, the Mugwort pollen-specific IgE was inhibited only up to 36% by Hazel nut. In immunoblotting inhibition experiments, Hazel nut partially inhibited all the Mugwort pollen bands, except that of the 19 kDa protein, whereas Mugwort pollen produced a nearly total inhibition of all the Hazel nut allergens (22).

Besides the major role played by Bet v 1 homologues in cross-reactivity among Birch pollen, Hazel nut and other foods and plants containing these substances, another allergen responsible for cross-reactivity between Birch pollen and Hazel nut is Hazel nut profilin (Cor a 2) – although the clinical relevance of this cross-reactivity has been questioned (15,23).

f17 Hazel nut

In some populations, the Hazel nut LTP (Cor a 8) is the major allergen. A Hazel nut LTP allergen has been identified that demonstrated a 62% identity with LTPs from Almond, 59% with Peach, and 59% with Cherry (7). Lipid Transfer Proteins have been reported to be very relevant panallergens, resulting in adverse reactions after the ingestion of botanically unrelated plant-derived foods. It has been suggested that, in view of the high prevalence and severity of the allergic reactions induced, Hazel nut, Walnut and Peanut should be regarded as potentially hazardous to patients sensitised to Lipid Transfer Protein allergens. (6,24-25).

Cor a 9, from Hazel nut, is an 11S globulin seed storage protein family member. This family comprises known food allergens in Peanut (Ara h 3) and Soya bean. The homology among these 3 proteins ranges from 45% to 50%. One known IgE-binding epitope of Ara h 3 shares 67% of homologous amino acid residues with the corresponding area of Cor a 9. The amino acids that differ were previously shown not to be critical for IgE binding in Ara h 3 (8).

Partial cross-reactivity has been reported to occur between Hazel nut and Macadamia nuts (26).

In a study of a patient with anaphylaxis to Coconut and oral symptoms to tree nuts, the presence of cross-reactive allergens between Hazel nut (a tree nut) and Coconut (a distantly related palm family member) was shown (27).

Allergy to Kiwi, Poppy seeds and/or Sesame seeds often occurs in patients with a simultaneous sensitisation to nuts and flour. In a study, the existence of both cross-reacting and unique components was observed; however, the cross-reacting and unique components could be different for different patients (28).

Clinical Experience

IgE-mediated reactions

Hazel nuts are a common cause of food allergy (29-30). In a study of 62 patients (adults and children) with nut allergy, Peanuts were the commonest cause of allergy (47), followed by Brazil nut (18), Almond (14), and Hazel nut (13,31). Allergies to Peanut (a legume) and tree nuts (Walnut, Hazelnut, Brazil nut, Pecan) frequently have an onset in the first few years of life, generally persist, and may account for severe and potentially fatal allergic reactions.

Some patients with allergy to Hazel nut may be allergic to the nut, others to the tree pollen, and still others to both. The type of allergic reaction and the specific allergens recognised can vary considerably from one geographic area to another (13).

Allergic reactions to Hazel nuts range from Oral Allergy Syndrome to severe anaphylactic reactions (8,32). Allergy to Hazel nut is most frequently observed in patients with allergy to Birch pollen. This can be explained largely by cross-reactivity of Bet v 1, the major Birch pollen allergen, with its homologue in Hazel nuts, Cor a 1. In addition, profilin and carbohydrate structures can be involved. Symptoms of food allergy in pollen-allergic patients are usually mild and restricted to the oral cavity, *i.e.*, Oral Allergy Syndrome. Allergy to Hazel nuts without concomitant pollen allergy is less common, but symptoms tend to be more severe and are often systemic (3,11,33-36).

The probability of patients with nut allergy having allergen-specific IgE to a particular combination of Peanut, Hazel nut and Brazil nut is similar, whatever the patients' age and sex. Multiple nut reactivity appears to increase with increasing age and may be due to the exposure of previously unchallenged sensitivity. The risk of a patient being sensitised to multiple nuts is sufficiently high that patients should always be tested for allergy to a range of nuts if they have a history of reacting to any nut (37).

Hazel nut-allergic individuals may react to very low doses of Hazelnut. A study reports that 29 Hazel nut-allergic patients had a positive reaction to increasing-dose challenges with Hazel nut. Itching of the oral cavity and/or lips was the first symptom in all cases. Additional gastrointestinal symptoms were reported in 5 patients, and difficulty in swallowing in 1 patient. Lip swelling was observed in 2 patients, followed by generalised urticaria in 1 of these. Threshold doses for eliciting subjective reactions varied from 1 mg up to 100 mg of Hazel nut protein (which would be found in 6.4 to 640 mg of Hazel nut meal) (38). Similar results have been reported in other studies. A study of a group of Hazel nut-allergic individuals indicated that 50% of the Hazel nut-allergic population will suffer from an allergic reaction after the ingestion of 6 mg (95% CI, 2-11 mg) of Hazel nut protein (8). But roasting of Hazel nuts significantly reduces their allergenic potential (3).

Allergic sensitisation may occur early on in life. In 163 infants aged between 1 and 12 months with symptoms of food allergy, IgE antibodies to Hazel nuts were detected in 68 (41.7%) (39).

In a study of 86 subjects (from Milan, Zurich, and Copenhagen) with a history of symptoms after Hazel nut ingestion, the diagnosis was confirmed in 67 (77.9%) on the basis of a DBPCFC. Of these subjects, 87% also had positive SPT to Birch pollen extract (40). Hazel nut was reported to have resulted in asthma in 2.7% of a study group following DBPCFC oral challenges to Hazel nut (41).

Grass allergy is the most common pollinosis in Northern Italy. Some patients with grass allergy show polysensitisation against other pollens and plant-derived foods. In these patients oral allergic syndrome (OAS) is frequently associated. In a study of 56 children suffering from respiratory allergy due to grass pollens, in the 16 patients with food allergy, Hazel nut was the major triggering food (50%), followed by Peanut (38%), Kiwi (31%), Apple and Walnut (19%) (42).

Severe systemic reactions such as anaphylaxis are possible with allergy to Hazel nut. In contrast to IgE binding patterns that occur in sera from patients with pollen-related Hazel nut allergy, low-molecular-weight (below 10 kDa) heat-stable proteins are responsible, as demonstrated in a young woman who experienced an anaphylactic reaction after the ingestion of Hazel nuts. She was not tree-pollen allergic. Suspect allergens in this size range include LTPs and 2S albumins (43). A Spanish study, evaluating 26 Hazel nut-allergic patients, including 10 who had experienced anaphylaxis, reported the lipid transfer protein to be the major allergen in Hazel nut allergy, including OAS and the more severe symptoms in the majority of patients (2). Food-dependant exercise-induced anaphylaxis has also been reported (44).

Urticaria to commercial Hazel nut skin cream has been reported in a 20-year-old girl who presented with anaphylaxis to String bean (45).

Hidden Hazel nut is a threat to allergic patients. (46) This may take the form of Hazel nut allergens in Hazel nut oil. Hazel nut or other nut oils may be used in chocolate manufacturing. The nut oil may pose a threat to patients with allergy, but this would depend on the method of manufacture and processing (47).

Occupational allergy to Hazel nuts is also a possibility. In a study of workers in candy and pastry manufacturing, SPT with food extracts used in the manufacturing of these products demonstrated that the most frequent positive results occurred with extracts of Cacao (31%), followed by reactions to chocolate (9%), cocoa (6%), Hazel nut (6%), and sugar (2%) (48).

In a study of 37 children with symptoms only of nocturnal enuresis who were investigated for allergy, IgE antibody evaluation showed that there may be a relationship between nocturnal enuresis and Soybean and Hazel nut food allergens. The authors cautioned that further studies were necessary to explain the underlying mechanisms and management of this disorder (49).

f17 Hazel nut

Other reactions

Nickel is abundant in Hazel nuts (50).

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f57 Japanese millet

Echinochloa crus-galli

Family:	*Poaceae* (*Gramineae*)
Common names:	Japanese millet, Cockspur, Barnyard grass, Sawa millet
Source material:	Peeled seeds
See also:	Common millet f55 and Foxtail millet f56

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Allergen Exposure

Geographical distribution

The name Millet is used to describe seeds from several taxonomically divergent species of grass. They are grown mostly in marginal areas and under agricultural conditions in which major cereals fail to give sustainable yields (1).

See common background for Millets on page 60.

Japanese millet and the other Millets are not closely related to Wheat.

Japanese millet is the fastest growing of all Millets and produces a crop in 6 weeks. It is grown in India, Japan and China as a substitute for Rice when the paddy fails. It is grown as a forage crop in the United States and can produce as many as 8 harvests per year. The height of the plant varies between 50 and 100 cm (1).

Environment

See common background for Millets on page 60.

The Millets are important sources of food for humans and animals. But in the West, with the exception of natural food stores, Millet is sold mainly as bird feed.

Unexpected exposure

See common background for Millets on page 60.

Allergens

No allergens from this plant have yet been characterised.

A number of proteins have been isolated and described as occurring in Japanese millet. The allergenic potential of these proteins was, however, not evaluated.

Barnyard millet, Common millet, Little millet, Foxtail millet, and Kodo millet were studied. The protein contents of the selected decorticated Millets were found to be 11.0, 12.3, 12.9, 10.5 and 10.6% respectively. Prolamin is a major storage protein in Foxtail millet, whereas glutelin is a major storage protein in all the other Millets. A protein band at the molecular weight range of 20 kDa was found to be homologous in all except Proso millet (2).

A Foxtail millet glutelin of 60 kDa (MG60) has been isolated. The primary structure at the N-terminal end was almost identical to that of the granule-bound starch synthase (GBSS) proteins from Rice, Barley, Maize, Wheat and Potato. Common epitopes from these starch-storing cereals were corroborated by immunoblot analysis, strongly suggesting a close relationship (3).

f57 Japanese millet

In a study, the antigenic relationships among "minor Millets" (Barnyard, Little and Foxtail millets) and other cereals (Wheat, Maize, Rice, Sorghum, Finger millet and Pearl millet) were evaluated using an antibody raised against a 20 kDa prolamin from Kodo millet. It was demonstrated that the prolamin was related to the prolamins from the other plants. Rice was the only common cereal that did not cross-react immunologically with the 20 kDa prolamin of Kodo millet (4).

A subtilisin inhibitor has been isolated from seeds of Foxtail millet. (5)

Proteinase inhibitors (trypsin/chymotrypsin) have been demonstrated to be present in Finger millet, Sorghum, Pearl millet, Foxtail millet, and Japanese millet (6). The amino acid sequence of an isolated trypsin inhibitor (7) had a high degree of homology to Bowman-Birk type inhibitors from leguminous and gramineous plants (8).

Cross-allergenicity among Rice, Wheat, Maize, Japanese millet and Foxtail millet was examined by IgE antibody determination and RAST inhibition studies, and significant close correlations among the 5 cereal grain extracts were demonstrated. A Rice protein of 16 KDa was shown to be one of the major allergens in Rice grain extracts (9-10). The protein showed sequence homology to Wheat alpha-amylase inhibitor and Barley trypsin inhibitor (11). The clinical relevance of this protein was not assessed.

Potential cross-reactivity

A Rice protein of 16 kDa has been shown to be involved in cross-allergenicity among antigens in Rice, Wheat, Maize, Japanese millet and Foxtail millet (10). The clinical relevance of this allergen was not examined.

Clinical Experience

IgE-mediated reactions

Hypersensitivity to cereals may occur via inhalation or ingestion. But reported allergy to Japanese millet is rare.

With the increasing popularity of "natural foods", Millet is more frequently included in various dishes, which might raise the incidence of Millet-related allergic reactions. Patients with adverse reactions to Gluten may substitute Millet for gluten-containing cereals.

Several studies of adults and children with atopic dermatitis and/or respiratory disease revealed the presence of IgE antibodies to Japanese millet (9,12-15).

Other reactions

Crude extracts of Millet may contain aflatoxins (16).

Millet diets rich in C-glycosylflavones are goitrogenic (17).

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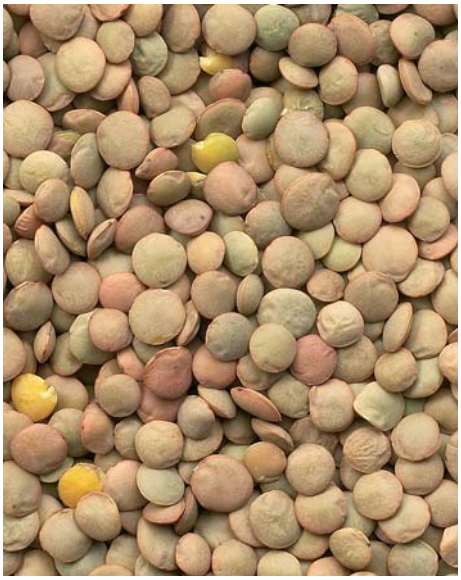
f235 Lentil



Lens esculenta

Family:	*Fabaceae* (*Leguminosae*)
Common name:	Lentil
Source material:	Dried seeds
Synonyms:	*Lens culinaris*, *Cicer lens*, *Lentilla lens*

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Allergen Exposure

Geographical distribution

Lentils are annuals with flattened edible seeds just a few millimetres in diameter. Lentils were cultivated by the Persians and Egyptians from 2500 BC. Lentils are now cultivated in most warm and subtropical regions of the world. Popular in parts of Europe and a staple throughout much of the Middle East and India, this tiny, lens-shaped, high-protein pulse, said to be the most nutritious of the pulses, has long been used as a meat substitute.

Environment

Lentils are usually dried for storage, transport and sale. They may be used in soups, salads and casseroles, and as dhal, and ground into cereal flour for enriching other flours or infant food. Lentils need to be boiled for 15 minutes to destroy harmful toxins found in the skin.

The young seedpods can be eaten raw or cooked like Green beans. Lentils are more digestible than many legumes. They are high in protein (but low in fat) and have a fair amount of minerals and vitamins.

The seeds are mucilaginous and laxative. They are considered helpful in the treatment of a variety of intestinal afflictions. Made into a paste, they are used as a cleansing application for indolent ulcers.

Allergens

The following allergens have been categorised:

Len c 1, a 12 to 16 kDa protein, a major allergen, corresponding to gamma-vicilin storage proteins (1-5).

Len c 2, a 66 kDa protein, corresponding to seed-specific biotinylated protein (1-2).

The isoforms Len c 1.0101, Len c 1.0102, Len c 1.0103 and Len c 2.0101 have been characterised.

Both Len c 1 and Len c 2 have been isolated from boiled Lentils. Heat treatment of Lentils was shown to result in drastic changes in the electrophoretic pattern, a strong increase of low-molecular-weight bands of 12 to 16 kDa proteins, and a decrease or disappearance of protein bands in the 25 to 45 kDa range. Len c 1 was shown to bind to 68% of the individual sera of Lentil-allergic individuals tested, whereas Len c 2 reacted with 41% of individual sera of this group (1).

Len c 1.01, a 48 kDa protein, has been characterised. Two of its processing fragments, corresponding to subunits of 12 to 16 kDa (previously named Len c 1) and 26 kDa, were shown to also be relevant

Lentil IgE-binding proteins. The purified allergen was recognised by 77% (17/22) of the individual sera from patients with Lentil allergy. Three isoforms were isolated, varying in their degree of N-glycosylation. There was a greater than 50% amino acid homology with Peanut and Soy vicillins (5).

Although many legumes appear to have both heat-labile and heat-stable allergens, a common feature of most legume allergens is their natural resistance to thermal, chemical, and, in some respects, proteolytic denaturation (6). The process of heating results in a significant decrease in IgE antibody binding, and IgE inhibition studies showed that the boiled Lentil extract had a greater inhibitory capacity than the crude extract. Immunoblots revealed no important differences in IgE binding patterns between the 2 extracts. Multiple allergens have been detected in a wide range of molecular mass, and boiled Lentil extracts maintained strong allergenicity (7). But further evidence for the heat alteration of the allergenicity was demonstrated in studies that concluded that Lentil extracts for the diagnosis of Lentil hypersensitivity should be heated, since these best identify clinically sensitive individuals (8).

Lentil-allergic patients who had developed a tolerance to Lentil ingestion were shown to have lower IgE antibody levels than symptomatic patients (7).

A lipid transfer protein has been isolated from germinated Lentil seed (9). Its potential allergenicity was not evaluated.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact is not seen frequently (10). In an *in vitro* study, the IgE antibody binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be immunochemically frequent, and most marked between the extracts of Peanut, Garden pea, Chick pea, and Soybean (11). However, clinical studies have found that there is little cross-reactivity among members of the legume family (12-14).

In contrast with the typical diet of most other Western countries, legumes are an important ingredient in the Mediterranean diet, and it is therefore not surprising that among Spanish children, sensitivity to legumes is the fifth most prevalent food allergy. Lentil and Chick pea are the most frequent causes of allergic reactions to legumes in Spanish children. Legumes have structurally homologous proteins, but they are not all equally allergenic. *In vitro* and *in vivo* tests may not predict cross-reactivity or clinical relevance. In a study of 39 Spanish children challenged (open or simple blind) with 2 or more legumes, the majority had symptoms with more than 1 legume. Thirty-two (82%) reacted to 2 or more legumes: 43,5% to 3, 25,6% to 2, and 13% to 4 legumes. Seventy-three per cent of the patients challenged with Lentil and Pea had positive challenges to both, 69,4% to Lentil and Chick pea, 60% to Chick pea, and 64,3% to Lentil, Chick pea and Pea simultaneously. Peanut allergy can be associated with allergy to Lentil, Chick pea and Pea, but less frequently. In contrast, White bean, Green bean and Soy were well tolerated by children allergic to other legumes. A high degree of cross-reactivity appeared to exist among Lentil, Chick pea, Pea and Peanut, on evidence from inhibition experiments. In this study, 82% of the children allergic to legumes were also sensitised to pollen. Pea and Bean were more likely to have *in vitro* cross-reactivity with *Lolium perenne*, *Olea europea* and *Betula alba*; the authors suggested that this was a result of common antigenic determinants or the coexistence of pollen and legume allergy (15).

Similarly, in another Spanish study, symptomatic hypersensitivity to Chick pea was frequently associated with Lentil allergy (16). Cross-reactivity or co-sensitivity was also observed among Blue vetch (Chickling pea), Chick pea, and Lentil (17). Similarly, shared allergenicity has been shown among blackgram, Lentil, Lima bean and Pea (18).

Panallergens or common protein families (*e.g.*, vicilins) may result in cross-reactivity among foods. Amino acid sequences deduced from 2 clones of the Lentil allergen Len c 1.02 were shown to have greater than 50% identity with the major Peanut allergen Ara h 1, and with Soybean (conglutinin

subunits), which are allergens belonging to the vicilin family (5). Similarly, in a study of 18 Spanish patients with Pea allergy, allergic reactions to ingestion of Pea were frequently associated with Lentil allergy. Vicilin and convicilin were shown to be potential major allergens from Pea, and these cross-reacted with the major Lentil allergen Len c 1 (4). Similarly, analysis of the epitopes and vicilin allergens Ara h 1 from Peanut, Len c 1 from Lentil, and Pis s 1 from Pea were shown to be similar, readily accounting for the IgE-binding cross-reactivity commonly observed among the vicilin allergens from these edible legume seeds (3).

Clinical Experience

IgE-mediated reactions

Lentil is the most common legume implicated in allergic reactions in food-allergic paediatric patients in the Mediterranean area and in many Asian communities. Approximately 20% of patients allergic to these legumes present with severe and systemic symptoms, although isolated cutaneous reactions are most common (5). Lentils are ranked fourth as a cause of hypersensitivity reactions in Spanish children, fifth in India. There are several reports in the literature of allergic symptoms caused by Lentil (8,19-20). In a Spanish study, 10,1% of 355 paediatric patients with food allergy had a convincing history of allergy to Lentils, and urticaria and oral allergy syndrome (OAS) were the most frequent symptoms. The symptoms may develop after ingestion of cooked Lentil and/or after inhalation of steam from boiling Lentil. Symptoms include angioedema, urticaria, asthma and anaphylaxis (1,16).

In a Spanish study, in 20 of 22 subjects who experienced allergy symptoms following exposure to Lentil, the most frequent symptoms were oropharyngeal ones (40%) and acute urticaria (30%); 3 patients also reported symptoms when they were exposed to steam from cooked Lentil. Onset of sensitisation occurred at less than 4 years of age, and 9 patients had allergic reactions to other legumes: Chick pea (6 patients), Pea (2 patients), and Green bean (1 patient) (21). Similar symptoms, *i.e.*, urticaria, angioedema, abdominal symptoms, rhinoconjunctivitis and asthma, following ingestion or inhalation of vapours from cooked legumes (Lentil, Bean or Chick pea) have been reported, but Lentil was found to induce the most severe reactions (22).

In an Indian study based in Delhi, the relevance of serum total and IgE antibodies was investigated in asthmatics with food sensitisation. Out of 216 consecutive patients, 172 were found to have elevated serum total IgE. Rice elicited marked positive skin prick test reactions (SPT) in 24 (11%) asthma patients, followed by Blackgram with 22 (10%), Lentil with 21 (9.7%) and Citrus fruits with 20 (9.2%) (23).

Four episodes of anaphylaxis occurred in an 8-year-old girl, which could be attributed to Lentil. These episodes occurred between the ages of 3 and 7 years. The first 3 involved ingestion of cooked Lentil and each episode required smaller amounts to induce symptoms. The fourth episode occurred with exposure by inhalation to cooking Lentil soup. Skin reactivity and serum IgE antibodies to Lentil were confirmed (24). Severe reactions may occur in adults. A 20-year-old man experienced episodes of asthma when exposed to the steam from cooking either Chick pea or Lentil. Type I hypersensitivity was demonstrated by means of serum IgE, skin reactivity, histamine release tests, and RAST inhibition. Specific bronchial challenges with the heated (75 °C for 30 minutes) extracts of Chick pea and Lentil elicited an immediate response (25).

Other reactions

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe cell-mediated gastrointestinal food hypersensitivity typically provoked by Cow's milk or Soy. A study reported on other foods causing this syndrome: 14 infants with FPIES caused by grains (Rice, Oat, and Barley), vegetables (Sweet potato, Squash, String beans, Pea), or poultry (Chicken and Turkey) were identified. Symptoms of typical FPIES are delayed (median: 2 hours) and include vomiting, diarrhoea, and lethargy/dehydration. Eleven infants (78%) reacted to >1 food protein, including 7 (50%) who

reacted to >1 grain. Nine (64%) of all patients with solid food FPIES also had Cow's milk and/or Soy FPIES. Initial presentation was severe in 79% of the patients, prompting sepsis evaluations (57%) and hospitalisation (64%) for dehydration or shock. None of the patients developed FPIES to maternally ingested foods while breastfeeding unless the causal food was fed directly to the infant. (26) Similarly, 6 patients (4 males, 2 females, aged 3-12 months) were diagnosed with FPIES triggered by foods other than Cow's milk and Soy: Chicken in 4, Turkey in 2, Pea in 1, and Lentils in 1. (Five patients reacted to more than 1 food type.) All reactions developed within 2 hours of ingestion of the allergenic food (27).

If Lentils are to be eaten whole, they must be boiled an extra 15 minutes to destroy harmful toxins found in the skins.

Aspiration of leguminous vegetables can cause a granulomatous pneumonitis, know as Lentil aspiration pneumonia, that manifests on radiological studies with small, poorly defined nodular opacities (28).

The Lentil pest *Bruchus lentis* was reported to have resulted in occupational asthma in an agronomist (29). In a more recent study of 16 patients with asthma and anaphylaxis as a result of inhalation of Lentil particles or ingestion of Lentils, SPT was positive to infested Lentils and *B. lentis* in all patients and negative to noninfested Lentil extracts. Five asthmatic patients were positive on bronchial challenge tests for Bruchus extract. Oral challenges performed with boiled infested Lentils were positive in 6 of 7 patients. These patients had no IgE antibodies to Lentil-specific proteins. The Lentil pest *B. lentis* can therefore be a cause of IgE-mediated rhinoconjunctivitis and asthma in patients eating or inhaling infested Lentil particles (30).

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Phaseolus lunatus

Family: *Fabaceae* (*Leguminosae*)

Common names: Lima bean, Butter bean, Sugar bean, Haba bean, Pallar bean, Burma bean, Guffin bean, Hibbert bean, Sieva bean, Rangoon bean, Madagascar bean, Paiga, Paigya, Butterpea, Prolific bean, Civet bean

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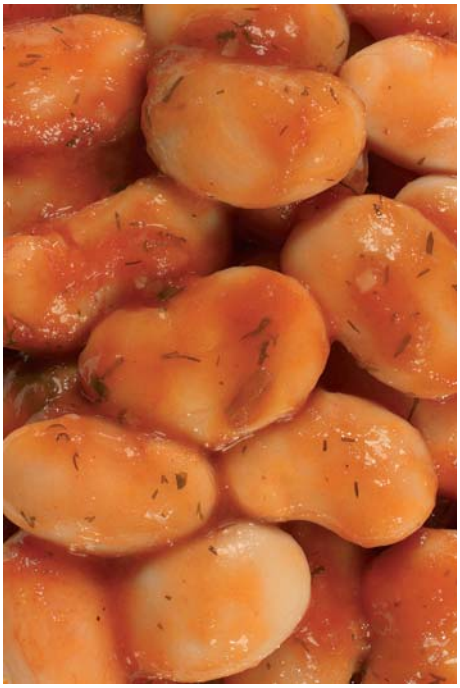

Allergen Exposure

Geographical distribution

Lima bean is a legume (1). Its seed is eaten as a vegetable. It is of Andean and Mesoamerican origin. The genus *Phaseolus* includes Lima, garden, snap, string, navy and pinto beans.

Lima plants produce pods that are up to 15 cm long and contain seeds that at maturity are 1 to 3 cm long and oval- to kidney-shaped. The seeds are usually quite flat but in some varieties are more spherical in shape. Immature seeds are uniformly green. At maturity, the most common variety produces white seeds, although black, orange, red and mottled seeds are seen.

"Butter bean" is the widespread term for a large, flat, white variety of Lima bean (P. *lunatus var. macrocarpus*, or *P. limensis*). In the southern United States, the smaller Sieva type are traditionally called Butter beans (or the Dixie or Henderson type). In that area, Lima beans and Butter beans are seen as 2 distinct types. In the United Kingdom, a "Butter bean" is a dried bean that can be re-hydrated, or a canned bean ready to use. In culinary terms, Lima beans and Butter beans are distinct, the former being small and green, the latter large and yellow (2).

Lima bean contains a number of anti-nutrients. Raw Lima beans contain cyanide, trypsin inhibitor, lectin, phytin and tannin. Soaking, autoclaving and toasting completely eliminated trypsin inhibitor and lectin, while it significantly reduced the levels of phytin, tannin and cyanide. Except for tannin, autoclaving for 20 minutes was found to eliminate all the other anti-nutrients in Lima bean (1). Lectin-related polypeptides are a class of defence proteins found in seeds of *Phaseolus* species, including in Lima bean (3). Lectins react indistinctly with erythrocytes of the ABO blood system; however, the lectin of Lima bean is specific to the blood group type A (4).

Lima beans contain linamarin, a cyanogenic glucoside, although the beans are rendered safe when cooked, and low-linamarin varieties are typically used for culinary purposes. Cyanogenic glycosides are present in green plant tissue as well as in seeds such as Almonds, flax seed, and wild Lima beans (5).

f182 Lima bean

Allergens

Early studies demonstrated that Lima bean contains at least 23 proteins that may have allergenic potential (6).

In a survey of food allergy among asthma and rhinitis patients in Delhi, India, evaluation of sera of patients with evidence of Lima bean skin reactivity demonstrated 12 IgE binding proteins of 18-96 kDa in Lima bean (7-8).

More recently, a study examining the *in vitro* cross-reactivity of Mesquite pollen and Lima bean demonstrated the presence of 20, 26, 35, 66 and 72 kDa proteins as shared IgE binding components between the 2 extracts (8).

Other proteins of unknown allergenic potential have previously been isolated; they have been shown to have allergenic potential in other plants. These include a 20 kDa cysteine proteinase inhibitor with an N-terminal sequence homologous to other members of the cystatins. The protein was relatively heat-labile, which suggested it could be inactivated with normal cooking (9). A trypsin inhibitor was isolated (10) and shown to be very thermostable, retaining activity even after boiling for 10 minutes (11).

Potential cross-reactivity

There are reports suggesting, based on SPT, that Lima bean cross-reacts with other allergenic legumes, such as Soya, Peanut, and black gram (6,12-13).

However, previous studies have demonstrated that, although the degree of biochemical cross-reactivity among members of the legume family is high, the clinical significance of this is low, so that being allergic to one legume does not necessarily require excluding other legumes from the diet. Results of skin prick tests alone should not be used for prescribing prolonged food restriction diets (12).

This is also suggested by a study reporting that only 2 of 41 legume-allergic patients (diagnosed by double-blind, placebo-controlled oral food challenge or "convincing history" of anaphylaxis) had an IgE-mediated hypersensitivity reaction to more than a single member of the legume family, even though extensive immunologic cross-reactivity was demonstrated among legume antigens in *in vitro* and *in vivo* assessments of 6 legumes (Peanut, Soybean, Lima bean, Pea, garbanzo bean and Green beans) (6).

The particular allergen within a legume will probably determine the extent and degree of cross-reactivity. This is illustrated by a report of a patient who suffered adverse reactions when eating Peas, Lentils, Peanuts, Kidney, Lima and navy beans; he experienced the most severe episodes following ingestion of Soybean products. A IgE antibody response to the Kunitz Soybean trypsin inhibitor polypeptide was demonstrated (14).

IgE-mediated food allergy often develops as a consequence of allergic sensitisation to pollen proteins. Recently, cross-reactivity was demonstrated between Mesquite tree pollen (*Prosopis juliflora*) and Lima bean as a food, both members of the family *Leguminosae* (*Fabaceae*).

In a study of 110 patients with asthma and/or rhinitis, of whom 20 showed marked positive reactions with *Prosopis* pollen extract, 12 patients showed elevated IgE antibody level to *Prosopis* pollen extract alone and 4 to both P*haseolus* and pollen extract. *P. lunatus* extract could inhibit IgE binding to *P. juliflora* in a dose-dependent manner. The presence of 20, 26, 35, 66 and 72 kDa proteins as shared IgE binding components between the 2 extracts was demonstrated (8).

A study reported on a 33-year-old woman who developed tongue swelling and burning and mouth itching within minutes of eating baked beans. Similar symptoms occurred following ingestion of other legume products, including Peas, a bean burrito, and Kidney and pinto beans. SPT was positive to Red kidney and White beans but not to Pea, string or Lima beans, confirming that cross-reactivity between the legumes is not absolute (15).

Clinical Experience

IgE-mediated reactions

Lima bean may induce symptoms of food allergy in sensitised individuals, although this is uncommon (12-13).

However, a number of studies have demonstrated sensitisation to Lima bean. In a survey of food allergy among asthma and rhinitis patients in Delhi, India, when allergy to Lima bean was claimed on history, sensitisation to Lima bean using SPT was demonstrated in approximate 3-4% (16) of 470 cases. Immunoblot analysis with allergic patients' sera confirmed and demonstrated the presence of IgE binding proteins in Lima bean (7).

In a study that investigated the *in vitro* cross-reactivity of Mesquite pollen and Lima bean, of 110 patients with asthma, rhinitis or both, 20 were shown to have IgE antibodies to Mesquite pollen extract; and of these, 12 patients showed elevated IgE antibody level to Mesquite pollen extract alone, and 4 to both Lima bean and pollen extract (8).

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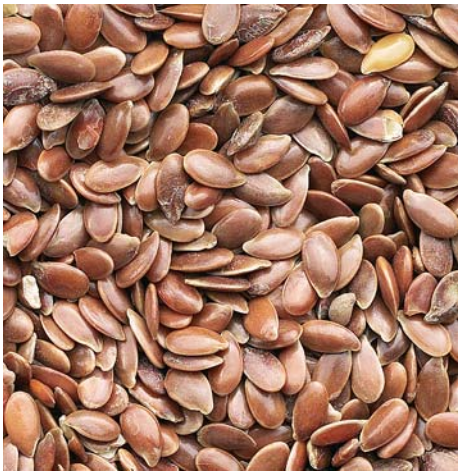
f333 Linseed



Linum usitatissimum

Family: *Linaceae*

Common names: Linseed, Flaxseed

Source material: Dried seeds

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Allergen Exposure

Geographical distribution

Flax has been cultivated and has grown semi-wild wild in various temperate and tropical regions for so many centuries that it is not even clear which hemisphere the plant originated from. Egyptians, Hebrews, Greeks, Romans and New World civilisations used the seeds as food and the fibres (flax) for textiles.

Flax is an annual, 0.3-1 m high, wiry, more or less branching plant with small, unstalked, dark or grayish-green leaves. The flowers are borne on the ends of the stalks. Each flower produces a round capsule in which 1 to 10 seeds develop. There are different cultivars for the production of Linseed oil and flax. Linseed plants are shorter, and their flowers are commonly bright blue, less commonly pale blue or white, while most flax cultivars bear white flowers.

Environment

Linseed is a common food in North Europe. It is often used in cereals and breads, including the German Leinsamenbrot. It can be sprouted and served in salads. It is also an ingredient in cattle feeds. Linseed meal may be what is left over from the oil extraction process, or it may be part of the "oil cake" because the hull is highly nutritious.

The seed contains 30 - 40% oil, which comprises mainly linoleic and linolenic acids. It is used mainly in the preparation of varnish, paint, linoleum, and soap. Linseed oil has recently been used as a laxative.

Flaxseed has experienced millennia of medicinal usage, mainly as a laxative, expectorant and demulcent. Recently, it has been noted that Linseed contains phytoestrogens, compounds with weak estrogenic or antiestrogenic activity, which have purported health benefits such as mitigation of hormone-dependent breast and prostate cancers, osteoporosis, cognitive dysfunction, cardiovascular disease, immune system dysfunction, inflammation, and infertility (1).

Flaxseed has recently gained particular attention in the area of cardiovascular disease. It not only contains lignans, a phytoestrogen. It is also the richest known source of alpha-linolenic acid (ALA), the parent compound of the omega-3 fatty acids. (In comparison, fish contain only trace amounts of ALA, and fish oil can adversely affect the taste and odour of food products.) It is, furthermore, rich in soluble fibre (2).

Unexpected exposure

Linseed may be "hidden" in cereals, milk from cows fed flax, laxatives (Flaxolyn, etc.), shampoo, hair tonic, infusions, depilatories, cattle feed, dog food, patent leather, insulating materials, carpets, cloth, cough remedies, breads, health shop muffins, and other "health food" products (3-5).

Allergens

Linseed contains potent allergens (6), but no allergens from this plant have yet been characterised.

Five allergens with molecular weights of 38, 35, 30, 22, and 20 kDa have been detected (5). However, in another study, allergens with a higher molecular weight (150-175 kDa), intensely bound with IgE, were found, as were other more discrete bindings with lower molecular weight allergens (90-100 kDa). Under reducing conditions, the high-molecular-weight bands disappeared and discrete bands of lower molecular weight (25-100 kDa) were detected (7).

In a study, the major allergen of Linseed was implicated in the case of a 39-year-old woman who developed anaphylaxis to Linseed grains; this allergen was shown to be a dimmer, consisting of a pair of 28 kDa monomers bound by SH2 groups. The authors suggest that the candidate may be malate dehydrogenase MDH-1, found in flax seeds (8).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but has not been clinically recorded (9).

Clinical Experience

IgE-mediated reactions

Linseed may uncommonly induce symptoms of food allergy in sensitised individuals; but cases could increase in number and variety because of the increased use of Linseed in bread and laxatives, and in a range of products from health food shops (3).

Anaphylaxis induced by Linseed ingestion was described in a 39-year-old woman who developed symptoms immediately after the ingestion of the first spoonful of Linseed grains prescribed as a laxative. Skin reactivity and IgE antibodies to Linseed was demonstrated (3).

A 40-year-old man had had, over a 6-year period, 5 or 6 episodes of intestinal/abdominal pain, vomiting, diarrhoea, generalised urticaria, acute dyspnoea without bronchospasm, hydrorrhoea, successive sneezing, nasal obstruction, pruritis, and intense general malaise which required emergency treatement, all occurring within 2-3 minutes after ingestion of multigrain bread. SPT and IgE antibody determination were positive (7).

Anaphylaxis in a 40-year-old woman was reported to be caused by the ingestion of Linseed oil used as a laxative. Ten minutes after the intake of the first spoonful, she experienced ocular pruritus and weeping, followed by strong palmar pruritus and generalised urticaria, nausea, and vomiting. SPT and IgE antibody determination were positive (5).

In 102 patients initially diagnosed with idiopathic anaphylaxis and then evaluated with a battery of 79 food-antigen skin prick tests, 10 different antigens provoked anaphylaxis, including Linseed. The study concluded that around 7% of the patients in question who were suspected of "idiopathic" anaphylaxis on the basis of history were not truly idiopathic (10).

Occupational dermatitis caused by Sunflower seeds and Linseed has been reported (11).

Other reactions

Flax is an important cause of respiratory disease. Non-IgE-mediated byssinosis, caused by inhalation of dust in the processing of flax, has been described in flax workers (12), as well as IgE-mediated occupational asthma from the processing of Linseed oil (13). (Byssinosis, a respiratory disease also caused by dust of cotton and soft hemp, is classically characterised as shortness of breath, cough, and chest tightness on Mondays or the first day of return to work after other time off (14)). Flaxseed hypersensitivity was described by 2 different authors in the 1930s, 1 describing Flaxseed sensitisation in 6 individuals (4,15).

f333 Linseed

Linseed may be a source of cyanide exposure. Linseeds are cyanogenic, but toxic effects are unknown from normal conditions of manufacture, which involve high-temperature treatment or from traditional and moderate use by humans. Also, safer cultivars have been developed. (However, unprocessed whole seeds and Linseed cakes processed under low temperature can be toxic to animals.) The potential cyanide yield can vary from 4 to 12 mmol/kg. Linseed contains the same cyanogenic glucosides as Cassava. Authors have suggested that excess intake (via laxatives) may be dangerous (16).

The oil in the seed contains 4% L-glutamic acid, or MSG, and therefore might cause MSG-type reactions.

The seed is hard to digest and provokes flatulence.

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Lupinus albus

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Lupin, Lupine, Blue lupin, White lupin, Yellow lupin, Sweet lupin
Source material:	Dried seeds
Synonyms:	*L. sativus*, *L. termis*
See also:	Lupin w207

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Allergen Exposure

Geographical distribution

The Lupin is a member of the Legume family and the genus *Lupinus*, which includes 450 species. Four species are of agricultural interest: the White lupin (*Lupinus albus*), the Blue lupin (*Lupinus angustifolius*), the Yellow lupin (*Lupinus luteus*), and *Lupinus mutabilis*. A sulfur-rich transgenic variety is available for animal feed. Lupin flour is an excellent source of proteins, having a higher content of albumin (55.6%) than globulins (31.5%).

Lupin is cultivated globally, primarily for use as animal feed, but also to be ploughed under as a soil enhancer (1).

The Lupin is an annual growing to 1.2 m by 0.25 m, with conspicuous colourful flowers. It can grow wild, but has been cultivated for at least 2,000 years, probably starting in Egypt. It is a useful spring-sown green manure crop, especially on light soils.

It is important as a stock food. Up to the 1920s, when "Sweet lupin" crops were developed, the seeds required soaking before consumption to remove toxic alkaloids, but the new types are safe to eat without any processing.

Environment

The edible seeds (from cultivated varieties of the plant) are employed as a protein-rich vegetable or savoury dish in all of the ways that cooked beans are used. They can also be roasted or ground into a powder and mixed with cereal flours. They have also used as a thickener of food products. Edible oil is obtained from the seed and the roasted seed is used as a coffee substitute. The seed is high in protein. Dried Lupin (usually called "lupini"), prepared by boiling Lupin seed, is a traditional snack (like Peanuts) in some Mediterranean countries.

Certain countries, *e.g.*, France, allow Lupin flour to be added to ordinary food such as bread (2).

If the seed is bitter, this is due to the presence of toxic alkaloids, and the seed should be thoroughly leached by soaking it and then discarding the soak water.

The seeds, taken internally, are diuretic, emmenagogue, hypoglycaemic and vermifuge. When bruised and soaked in water, they are used as a poultice on ulcers, etc.

Unexpected exposure

Lupin flour and bran are increasingly being used in food manufacturing, where they contribute protein, bulk, fibre, and some textural properties. Lupin may be regarded

as a "hidden" allergen. Inclusion of Lupin in Wheat flour was first permitted in the United Kingdom in 1996, and in France at the end of 1997 (1). Since then, Lupin flour and bran have been widely used in European countries such as France, the Netherlands, Italy, Spain and Germany, in bread, biscuits and other baked products, pasta, confectionery, Soya substitutes, and dietary and health foods. Bakery goods may contain up to 10% Lupin flour (3).

Lupin oil is used in making soap. A fibre obtained from the stems is used for making cloth and other products. See also under Environment.

Allergens

In an individual with allergy to Lupin, important allergenic proteins of 71, 59 and 34 kDa in size, along with less important 24 and 17 kDa proteins, were isolated (4). In another study of 2 individuals with Lupin allergy, strong differences in proteins in extracts of fresh and cooked seeds were demonstrated. Sensitisation to low-molecular-weight bands was demonstrated; a doublet of 9 and 10 kDa was found in raw and cooked seeds and was more clearly represented in skin than in pulp (5). A study reported the isolation of allergens that seemed to be in the 35 kDa to 55 kDa range and heat-stable, with a 21 kDa protein appearing to be a major protein (6). Another study reported a reduction in allergenicity after autoclaving at 138 °C for 20 minutes. In the case of IgE antibodies from 2 individual sera that had recognised allergenic protein bands at 23 and 29 kDa in samples autoclaved at 138 °C for 20 minutes, autoclaving for 30 min abolished the IgE binding to these 2 components. A previously undetected band at 70 kDa was recognised by an individual serum. The authors concluded that prolonged autoclaving might have an important effect on the allergenicity of Lupin for the majority of patients (7).

In a study that sought to identify allergens associated with Lupin allergy, 6 patients with a history of allergic reactions to Lupin flour were evaluated. Two patients allergic to Lupin but not to Peanut displayed IgE binding predominantly to proteins of approximately 66 kDa, and weak binding to 14 and 24 kDa proteins, whereas patients with both Peanut allergy and Lupin allergy showed weak binding to Lupin proteins of about 14 to 21 or 66 kDa (1). Similarly, in a study of 2 patients with oral allergic syndrome following Lupin ingestion, and no symptoms associated with Peanut or other legumes, sera IgE from both patients recognised proteins of approximately 34 kDa and in the 40-65 kDa range. The second patient's serum also recognised 7-15, 38, 77, 162 and 195 kDa proteins (8).

To date, the following allergens have been characterised:

Lup a 11S Globulin (1,9-11).

Lup a gamma Conglutin (9-14).

Lup a beta Conglutin (1,9,11,13-14).

Lup a Vicilin (1,11).

Lup a LTP, a lipid transfer protein (15).

A 2S albumin has been isolated (10,16). The 2S albumin fraction appears to consist of a number of isoforms ranging from 4 to 11 kDa (16-17). However, the 2S albumin, unlike 2S albumins from other seeds, may be non-allergenic (10).

Plant stress was shown to activate a class-III chitinase, designated IF3. The protein was detected in the seed, leaves and roots. In healthy, nonstressed tissues of the plant a thaumatin-like protein was also detected, the presence of which researchers could not explain. Whether these proteins also occur in the pollen is unknown (18-19). Proteins that show similarity to PR-10 proteins have also been detected in the leaves (20). Although chitinase and thaumatin proteins have allergenic potential, their clinical significance in this plant has not been elucidated as yet.

A common feature of most legume allergens is their natural resistance to thermal, chemical, and in some ways proteolytic denaturation (21).

In an investigation of "hidden" Lupin seed in biscuits, chicken bouillon and a dehydrated chicken soup, a Lupin allergen with a molecular weight close to 14 kDa was detected (22).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Fabaceae* (legume family) could be expected but in fact does not occur frequently (23-24). In an *in vitro* study, the IgE binding to protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked among the extracts of Peanut, Garden pea, Chick pea, and Soybean (25). However, clinical studies have found little cross-reactivity among members of the legume family, with the possible exception of cross-reactivity between Lupin seed and Peanut (26-27).

In a study of 6 Lupin-allergic individuals, 3 were co-sensitised to Peanut and Lupin (1). But in a study of 2 patients with oral allergic syndrome following Lupin ingestion, investigations supported the conclusion that Lupin is capable of inducing allergic sensitisation without cross-reactivity with Peanut (8). Significantly, individuals may have substantial levels of Peanut-specific IgE without being clinically allergic to Peanut (28).

A study of the legumes Peanut, Soybean, Green bean, Pea, and Lima bean demonstrated that clinical hypersensitivity to one legume does not warrant dietary elimination of all legumes. The authors pointed out that results of SPT should not become the basis of prolonged food restriction diets (26). However, legume sensitisation may be a dynamic process, as described in a patient whose symptoms started with reactions to only a single legume (Chick pea) and who then progressively developed sensitisation to Lentil, White bean, Lupin, and Pea (24).

Cross-allergic clinical reactions to other members of the legume family such as Soybean and Lentils occur in about 5% of Peanut-allergic patients, but cross-allergic reactions were found to be 68% between Peanut and Lupin (26). Among 24 Peanut-allergic patients, SPT to Lupin flour were positive in 11 (44%). Oral challenges with Lupin flour were positive in 7 of 8 subjects with the same dose as of Peanut. The major Lupin flour allergen, a 43 kDa protein, was found to be present in Peanuts. RAST inhibition and immunoblot tests showed cross-reactivity of Peanut with Lupin flour and pollen. The authors felt that the risk of cross-reactive Peanut-Lupin allergy is high, contrary to the risk with other legumes (29). Similar results have been reported by other researchers; one study reported that 68% of a group of Peanut-allergic patients showed positive reactions to Lupin flour when tested (6,30-31). Subjects with positive SPT to Lupin also reported a history of reactions to Green pea (6).

In a study of severe anaphylaxis to Almond, a 45 and a 30 kDa protein isolated from Almond showed a 60% homology to the conglutin gamma protein from Lupin seed and to the 7S globulin from Soybean respectively. Immunoblot inhibition experiments were performed, and IgE binding to Almond 2S albumin and conglutin gamma was detected in the presence of cross-reacting Walnut or Hazel nut antigens (32). The clinical relevance of this finding was not established. There were similar findings in other connections, with 2S albumin from Sunflower seeds being reported to be homologous with albumin from Lupin seeds (conglutin delta) (17). The full clinical significance of these cross-reactions will require further elucidation. However, the 2S albumin, unlike 2S albumins from other seeds, may be non-allergenic (10).

A study using computer-aided amino acid sequence comparison and 3-dimensional modelling of the suspected cross-reactive proteins to compare their molecular surfaces reported highly significant sequence homology and molecular similarity between allergen Ara h 8 of Peanut and pathogenesis-related protein PR-10 of White lupin. Another protein of Lupin, the beta-conglutin precursor, was found to be significantly homologous to the Ara h 1 allergen of Peanut. The molecular surfaces of Ara h 8 and PR-10 were remarkably similar (13). The full clinical significance of this was not elucidated.

f335 Lupin seed

Clinical Experience

IgE-mediated reactions

Lupin flour may commonly induce symptoms of food allergy, allergic rhinitis and asthma in sensitised individuals after ingestion of the food or inhalation of the flour (2,7,22,24,33-40). Lupin flour in food has also been reported to produce urticaria and anaphylaxis (24,36,41). Case reports of individuals experiencing oral allergy syndrome to Lupin have been made (1,8,42). Contact urticaria elicited by Lupin has been reported (43-44).

The eliciting dose of Lupin flour may be very small. In a study of 6 Lupin-allergic patients, the eliciting dose for subjective symptoms (oral allergy symptoms) was 3 mg or less, and 300 mg or more for objective symptoms (1).

Lupin allergy may arise either by primary sensitisation, or by clinical cross-reactivity in Peanut-allergic persons (8,28,45). The prevalence of allergic reactions to Lupin flour or seed appears to be increasing along with the practice of adding protein-rich flour to bread. Because Lupin flour has gained favour mainly in Europe, Lupin flour allergy has been reported mainly in European patients. These are known to commonly be allergic to other legumes, particularly Peanut, Soya and Pea (37). The prevalence of Lupin allergy has increased markedly in some countries, especially France, where the addition of Lupin flour to Wheat flour was first permitted in 1997 (2). The first report of Lupin anaphylaxis there was in 1999 (3). In 2002, Lupin was the fourth most frequent cause of severe food-associated anaphylaxis reported to the French Allergy Vigilance Network. Two instances of anaphylaxis resulted from a chocolate drink containing Lupin flour. Both children were also allergic to Peanuts, and the authors attributed these reactions to cross-reactivity mechanisms (36). In a recent Portuguese study aimed at determining the prevalence of Lupin sensitisation in 1,160 subjects and utilising, among other tests, SPT to Lupin, a sensitisation rate of 4.1% was found. A 75% co-sensitisation rate was found between Lupin and legumes, 82.1% co-sensitisation between Lupin and pollen, and 28.5% co-sensitisation between Lupin and Latex (46).

Lupin allergy may also occur in young children (47). A 5-year-old girl with Peanut allergy experienced urticaria and angioedema after ingesting spaghetti-like pasta fortified with Lupin flour (6). In a child who had experienced anaphylaxis to Lupin flour, SPT was positive and *in vitro* cross-reactivity with other legumes was demonstrated, but this was shown to not be clinically relevant in this instance (24).

An 8-year-old asthmatic child, with allergy to Peanut, suffered an asthma attack while playing with his brother, who had been eating Lupin seed as a snack. SPT was positive to Lupin extract, Peanut, Garbanzo bean, Navy bean, Pea, Green bean, Lentil, Soybean, and a number of pollens. The prick-by-prick tests both from dried seeds and those preserved in salt and water were strongly positive. Serum IgE antibody level to Lupine was 1.43 kU_A/l, Peanut 4.32 kU_A/l, Soy 2.15 kU_A/l, Lentil 3.12 kU_A/l and Garbanzo 0.7 kU_A/l. A challenge with Lupin seeds resulted in asthma symptoms within 5 minutes of contact (35).

The first reported instance of an anaphylactic reaction caused by the ingestion of Lupin flour was that of a paediatric patient without a known Peanut allergy, an 8-year-old boy who developed nose and eye discharge followed by oedema of the face and difficulty breathing 30 minutes after eating a waffle containing Lupin flour. SPT was positive to Peanut, and a prick to prick test using Lupin flour was strongly positive. The IgE antibody level was raised for Lupin seed (20.8 kU_A/l) and Peanuts (> 100 kU_A/l) (28).

An interesting report was made of a 30-year-old technician who experienced repeated episodes of rhinitis, conjunctivitis and palpebral angiodema related to her handling of Lupin flour used for skin prick tests and oral challenges. She tolerated Peanuts (4).

Anaphylaxis was described in a 25-year-old Peanut-allergic woman after she ate a restaurant meal. During the meal, she developed pruritus of her mouth and lips,

and her tongue started to swell. Fifteen minutes later she had difficulty in breathing and her throat had "narrowed". Lupin was identified as the cause and had been present in the onion ring batter she had consumed. She had not previously had allergic reactions to Lupin. SPT and IgE antibodies to Lupin were positive (37).

A description of 3 individuals who experienced adverse reactions to Lupin highlights potential consequences of Lupin allergy. The first, a 42-year-old woman, developed acute urticaria and angioedema, with throat tightness and cough, after a meal that included a bread roll. A more severe anaphylactic reaction, including marked breathlessness requiring oxygen and adrenaline, had occurred on another occasion following ingestion of the same type of bread roll. Lupin bran was a constituent of these rolls. SPT with saline extracts of the raw Lupin bran and of the baked bread roll were strongly positive, but negative for Soybean and Peanut. A mild generalised reaction followed ingestion of a specialty bread that was later found to contain Lupin bran. A second patient, a 42-year-old woman, was described who had developed acute abdominal discomfort, urticaria, facial oedema, cough and shortness of breath 10-15 minutes after eating a bread roll that contained Lupin bran. SPT was positive to an extract of Lupin bran. The third patient, a 26-year-old woman who had often eaten lupini (boiled and dried Lupin in the form of a snack food), on one occasion, after eating commercially prepared lupini from a jar, developed urticaria, angioedema and respiratory difficulty, requiring hospitalisation. Subsequently, a similar but less severe reaction occurred after she ingested a small portion of home-prepared, boiled and salted lupini. She had also experienced urticaria and angioedema after eating ginger biscuits, which were subsequently found to contain Lupin flour. SPT was strongly positive to a Lupin bran extract, and her IgE antibody level was 12.9 kU_A/l (38).

A 24-year-old woman with Peanut allergy experienced acute swelling of the lips, urticaria and rhinoconjunctivitis on 4 separate occasions when eating a certain brand of hot dog bread containing Lupin flour (48).

A male patient reported several episodes of generalised angioedema after ingestion of snacks that included Lupin seeds. SPT was positive for a number of tree nuts as well as Sunflower seed. Skin reactivity was found against Lupin seed (both the skin and the pulp), and IgE antibodies was found to Lupin. The same report also described a female patient who had reported angioedema of the lip and generalised urticaria following ingestion of several Lupin seeds. She had previously eaten this snack on a number of occasions with no adverse effects. Skin reactivity was present for Maize flour, Hazel nut, Peanut, Walnut, Sunflower seed, Chestnut, Green bean, Tomato, Lettuce and Mustard. Skin reactivity was also found for Lupin seed (skin and pulp) and the Lupin IgE antibody level was raised (5).

A 52-year-old woman developed facial and mucosal oedema, followed by dizziness and shortness of breath, a few minutes after ingestion of a nut croissant containing Lupin flour; she required emergency care. The IgE antibody level for Lupin seed was 42.9 kU_A/l. SPT using Lupin flour was strongly positive. No evidence of cross-reactivity with Peanut could be detected through *in vitro* or *in vivo* tests (49).

Further evidence for the close relationship between Peanut allergy and Lupin allergy was demonstrated in a study of 24 Peanut-allergic patients, in whom SPT for Lupin flour was positive in 11 (44%). Oral challenges using the same dose as used with Peanut were positive in 7 of 8 subjects (29). A study reported acute asthma in a patient with allergy to Peanuts. SPT to raw and cooked Lupin flour was positive. The level of allergen-specific IgE to Lupin flour was high. An oral challenge test induced acute asthma at a dose of 965 mg of Lupin flour, an amount that may be found in 100g of bread (31). Researchers have stated that cases of isolated allergy to Lupin flour, without pre-existence of Peanut allergy as well as workplace asthma by inhalation, are rarely seen (30).

Occupational allergy may occur to Lupin, particularly in mill workers. A study reports on 3 workers who showed allergic symptoms to Lupin flour following inhalation. Skin reactivity to Lupin seed flour extract was present in all 3 patients, and Lupin-specific IgE antibodies were detected in 2 (50).

Other reactions

The seeds of many Lupin species contain bitter-tasting toxic quinolizidine alkaloids, though there are often sweet varieties within the same species that are completely wholesome. The alkaloid profiles are rather constant (51). Taste is a very clear indicator. Lupin seed alkaloids appear to be toxic mainly to animals and non-toxic to humans, although not all researchers are in agreement about this (52). Anticholinergic toxicity associated with the ingestion of lupini beans was reported in a 46-year-old female of Italian descent, who presented with blurry vision, dry mouth, facial flushing, and confusion. Symptoms had begun quite suddenly over the course of about 30 minutes, 3 to 4 hours after ingesting lupini beans. Lupini beans derive their bitter flavour from the high levels of quinolizidine alkaloids they contain and must undergo a de-bittering process of washing with water, a process that normally takes 4 days. (Some authors state that these toxic alkaloids can be leeched out by soaking overnight and discarding the soak water. It may also be necessary to change the water once during cooking.) The patient had soaked her lupini beans for only 36 hours before she ate several handfuls of them (53).

The number, type, and level of alkaloids are highly variable among species. In Southern Europe and the Middle East, high-alkaloid Lupines or "Bitter lupins" are grown. The primary crop cultivated in Australia is low-alkaloid Lupin or "Sweet lupin". The level of alkaloids remaining in European lupins after the de-bittering process is approximately 500 mg/kg, whereas the level of alkaloids in Sweet lupins is about 130 to 150 mg/kg (53).

Fungal toxins also readily invade the crushed seed and can cause chronic illness, usually in animals. Lupinosis is a mycotoxicosis caused by the ingestion of toxins produced by the fungus Phomopsis leptostromiformis, which grows on Lupine plants. Outbreaks of natural lupinosis may occur in lambs.

Ungerminated legume seeds (broad bean, Chick pea and Lupin) may contain biogenic amines. Tryptamine was the main biogenic amine detected, and its concentration increased considerably during germination. Beta-phenylethylamine was detected in small amounts, and its concentration slowly increased during germination. The concentration of tyramine showed a fluctuation pattern during germination in all tested legumes. Heat treatment seems to have little effect on the concentration of biogenic amines in legume sprouts (54).

A 7-year-old boy was operated on for intestinal obstruction due to a phytobezoar. He had eaten an exceptionally large amount of Lupin seeds a few hours before the onset of pain (55).

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f345 Macadamia nut

Macadamia spp.

Family: *Proteaceae*

Common names: Macadamia nut, Queensland nut, Australian nut

Source material: Shelled nuts

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Allergen Exposure

Geographical distribution

Macadamia nuts are the fruit of an Australian tropical evergreen tree, and are also known as Queensland or Australian nut. The tree was exported to Hawaii in the 1890's as a source of shade but subsequently became a crop. It is also grown in warm Mediterranean areas, in the southern USA and in South Africa. The seed grows on 2 species of trees (*M. tetraphylla* and *M. intergrifolia*). The commercial Macadamia tree (*M. intergrifolia*) grows more than 12 m tall and has creamy-white flowers.

The "nut" is not truly a nut but a seed (1). The round, whitish kernel is enclosed in an extremely hard, brown shell, about 2.5 cm in diameter and 2 to 3 mm thick. The shell is in turn contained in a fibrous green husk.

Australia is the world's largest producer of the nut. For 7 months of the year the nuts fall on their own and are harvested from the ground by hand and taken to the factory for processing. Workers ("nut sorters") stand beside the "shell" conveyer and pick out by hand salvageable nut kernels that have escaped the mechanical separators. The importance of this process for allergy consists in both the intense occupational exposure and the relative rarity and costliness of the nuts. The kernels are then dry- or oil-roasted (2).

The nuts are richly flavoured and high in protein. Their oil content (70%) is higher than that of other nuts.

Environment

Macadamias can be consumed fresh or roasted and are added to a variety of foods, including snack bars, cereals, and nut mixes. Ground Macadamia meal is becoming an increasingly popular ingredient in baked goods, as is cold pressed Macadamia oil (3).

Allergens

No allergens from this plant have yet been characterised.

A 17.4 kDa protein appears to be the major allergen and is present in raw and roasted extracts (4).

A vicillin with anti-bacterial properties has been isolated, but its allergenicity was not determined (5).

Potential cross-reactivity

Macadamia nut belongs to the *Proteaceae* family, which are classified separately from most other tree nuts and from Peanuts.

Partial cross-reactivity has been reported between Hazel nut and Macadamia nut (4). In a study of Almond, antibodies developed to Almond were shown to be specific for Almond; however, some cross-reactivity was observed with extracts of some tree nuts and

of Sesame seeds. Sodium dodecylsulfate-polyacrylamide gel electrophoresis and Western immunoblotting indicated that anti-Almond antibodies recognised proteins extracted from Black walnuts, Brazil nuts, Cashews, Hazel nuts, Macadamia nuts, Pistachios, and Sesame seeds, in addition to those from Almond (6).

Clinical Experience

IgE-mediated reactions

Macadamia nut, although not as common a food as many other tree nuts, may occasionally cause serious allergic reactions in sensitised individuals. Cases are perhaps becoming more frequent because of the increasing use of Macadamia nuts, alone and in other products (7-8). In particular, Macadamia nut is becoming more frequently available in nut mixes and is being sold in countries which did not previously import it.

In an American study of 115 patients aged 4-19.5 years, moderately severe reactions to Macadamia were reported in 3 (13%) individuals, and severe reactions in 2 (4%) (9). In a telephonic survey, of 118 subjects reporting an allergy to Peanut or tree nut, 2 self-reported allergy to Macadamia nut (10).

Macadamia nut-induced uvular angioedema, angioedema of the posterior part of the tongue, dysphagia, chest tightness, chest pain, and chest pruritis were described in a 36-year-old man. Symptoms occurred 5 minutes after eating a single chocolate-covered Macadamia nut. A prick to prick test with fresh Macadamia nut was positive (11).

A study reported on 2 patients with allergy to Macadamia nut. A 48-year-old woman reported oral allergy symptoms occurring within 10 minutes of ingestion of 6-8 Macadamia nuts, followed by palpitations, dyspnoea, dizziness, flushing and severe itch. Skin reactivity was detected. A 34-year-old man presented with tongue swelling, itchy, hot palms, swollen hands and throat tightness, which developed within minutes after eating a single Macadamia nut. SPT was positive (3).

Reactions may be severe and result in anaphylaxis (8,12). An 18-year-old woman had immediate oral itching when eating flourless orange cake made with Macadamia meal. Within 5 minutes, this reaction had progressed to anaphylaxis (4). Anaphylaxis following contact with Macadamia nut has been reported in an infant (13).

A 42-year-old man developed generalised pruritus, itching of the throat, rhinitis, dyspnoea and dizziness 5 minutes after eating a few roasted Macadamia nuts. Skin prick tests were positive to Hazel nut and roasted Macadamia nut but negative to Peanut, Almond, Brazil nut and Walnut. A 34-year-old man repeatedly developed severe oral burning, itching and swelling after eating Hazel nut, Walnut, Brazil nut, Almond and Macadamia nut, but tolerating Peanut and Cashew nut. SPT was positive to Peanut, Almond, Hazel nut, Brazil nut and Walnut but negative to Cashew nut. A prick-to-prick IgE determination was positive for Macadamia nut (14).

A 23-year-old female with a history of atopic dermatitis, allergic rhinitis, and allergic conjunctivitis reported that in her fourth year of primary school, she ate Macadamia nuts and developed oral discomfort and generalised urticaria. In her second year of junior high school, she ate Macadamia nuts and developed oral and pharyngeal discomfort, followed by generalised urticaria and dyspnoea. At the age of 20 years, she also developed oral discomfort after eating vegetables in a Chinese dish containing Macadamia nuts. SPT using Macadamia oil extract was positive. Although she developed oral allergy syndrome after eating Macadamia nuts, she was negative for Bet v 1 and Bet v 2 as allergens (15).

Nut oils may pose a threat to patients with allergy, depending on the method of processing. IgE reactivity to proteins in Macadamia oil has been reported, based in testing of sera from patients with Macadamia allergy (16).

Other reactions

Occupational dermatitis from Macadamia nut shells was described in 15 nut sorters at a Macadamia nut processing plant. The nature of the allergen was not found but was thought to be confined to the shell, as opposed to the plant leaf or kernal (2).

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f8 Maize/Corn

Zea mays

Family:	*Poaceae* (*Gramineae*)
Common names:	Maize, Corn, Sweet Corn, Indian Corn, Field Corn
Source material:	Untreated planting seeds
See also:	Maize, Corn g202

Cultivars within the genus may be divided into 6 general types: Popcorn (*everta*), Flint corn (*indurata*), Dent corn (*indenta*), Flour corn (*amylacea*), Sweet corn (*saccharata*) and Pod corn (*tunicata*).

There are, however, only 2 basic types: "Sweet corn" is distinguished from "Field corn" by the high sugar content of the kernels at the early "dough" stage and by wrinkled, translucent kernels when dry

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Allergen Exposure

Geographical distribution

Maize kernels grow on long "ears" at the leaf axils of this unusual plant. The original habitat was probably South America or Mexico, where Maize was the staple diet of the American Indian. Maize is now grown almost anywhere summers are reasonably warm, although approximately 50% of the world's Maize is produced in the USA. It is a staple cereal of the human diet in Central and South America and in many parts of Africa. It is extremely important in livestock rearing, food processing and other commercial activities in developed countries. Few plants are grown more extensively or put to more diversified uses than Maize.

Environment

In the US and Europe, Maize is used almost entirely for animal feeding, as grain or fodder. But it is important as a vegetable, and as the snack popcorn. Kernels may be eaten straight from the cooked cob or cut off and used in succotash, custards, fritters, soups and chowders. Kernels are also used in mixed pickles and vegetable relishes. Corn meal, grits, and hominy are prepared forms of Maize kernels. Maize is also converted into various substances that have a wide range of usage, such as starch, syrup, dextrin, oil, and zein. Maize serves in the making of whiskey and other alcoholic products, and condensed milk. The roasted seed is a coffee substitute. Riboflavin and nicotinamide are added to fortified Maize.

The various parts of the plant have been used in the treatment of a variety of ailments.

Unexpected exposure

See under Environment.

Allergens

Various allergens have been characterised:

Zea m 14, a 9 kDa lipid transfer protein (1-9).

Zea m 25, a thioredoxin (1,8,10-11).

Zea m 27kD Zein, a 27 kDa protein, a glutenin (12-13).

Zea m 50kD Zein, a 50 kDa protein, a glutenin (12).

The following allergens have been characterised in Maize pollen: Zea m 1, Zea m 2, Zea m 3, Zea m 4, Zea m 5, Zea m 12, Zea m 13, Zea m CBP, and Zea m Zm13m. See Maize pollen g202.

Zea m 14, a lipid transfer protein, has also been isolated from Maize flour. Skin reactivity and IgE antibodies to this allergen were detected in 19 of 22 patients (86%) with systemic symptoms following the ingestion of Maize, confirming this as the Maize major allergen (1). Maize lipid transfer protein is highly heat-stable, and even heat treatment at 100 °C for 160 minutes, though it almost totally eliminated the IgE-binding activity of the higher-molecular-weight bands seen in Maize, did not affect that of the lipid transfer protein (9).

Zea m 27kD Zein, a Maize zein, has been identified in an extensively hydrolyzed casein formula, Nutramigen. These proteins are water-insoluble and presumably originated from the Maize starch in Nutramigen. Although rabbits immunised with this formula developed antibodies against zeins but not against Cow's milk proteins, the clinical relevance of these proteins in Nutramigen remains to be established (13).

A 16 kDa allergen, recognised by 36% of Maize-allergic patients, was also isolated and shown to be the Maize inhibitor of trypsin (1).

A 22 kDa protein from Maize seed, with a 52% homology with the protein thaumatin and a 99% homology with the 22 kDa trypsin/alpha-amylase inhibitor, has been isolated (14). The allergenicity of this protein was not evaluated.

A 50 kDa allergen, belonging to the reduced soluble protein (RSP) fraction, has been isolated and shown to be stable to heat and digestion. In a study of 16 patients with specific IgE to Maize, only 6 patients were symptomatic. These 6 patients were DBPCFC-positive on challenges, and SPT with the purified RSP fraction was positive for all of the 6 DBPCFC-positive patients (15).

A protein similar to an isoflavone reductase (IFR) and/or an isoflavone reductase-like (IRL) protein has been isolated. (16) The allergenic potential of this protein was not determined.

In an individual with Maize dust-induced IgE-mediated occupational asthma and rhinitis, 10 IgE-binding components with sizes of 9 to 140 kDa were detected within the Maize dust extracts (17).

A chitinase has been isolated from Zea mays seeds (18). The allergenicity of this chitinase was not evaluated.

Maize seed contains the panallergen profilin, but at much lower levels than those found in Maize pollen (Zea m 12) and in foods such as Celery and Tomato (19). This profilin may be of low clinical significance, as heat processing destroys the protein. Nonetheless, the presence of profilin in Maize seed may play a role in occupational asthma where inhalation of Maize flour or dust is possible.

Normal Maize contains about 7-13% protein, which can be fractionated into various solubility classes. The salt-extractable fraction (albumins and globulins) mainly comprises proteins with metabolic functions. Extraction with aqueous alcohol isolates the prolamin fraction that contains the storage proteins of the seed. These constitute around 60-70% of the Maize endosperm proteins and are called zeins. These are various polypeptides, classified as alpha, beta, delta and gamma zeins. The reduced soluble proteins are alcohol-extractable and soluble in water. Also present is an alcohol-insoluble glutelin fraction (15).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (20). *In vitro* cross-reactivity among the IgE binding proteins of Maize, Rice, Soybean and Peanut was demonstrated. The high degree of cross-reactivity between Rice and Maize was thought to be due to the fact that they both belong to the same botanical family. But the authors were not able to clarify the clinical significance of these cross-reactivities and suggested further clinical studies to put these findings into perspective (21). An earlier study reported that, by using RAST inhibition tests, cross-antigenicity could be

demonstrated among different cereal grains, the degree of cross-reactivity closely paralleling their taxonomic relationship in the following order of decreasing closeness: Wheat, Triticale, Rye, Barley, Oat, Rice and Maize (22).

The major Maize allergen is a lipid transfer protein (7,23). A high degree of cross-reactivity has been demonstrated among the LTPs of Peach, Apple, Walnut, Hazel nut, Peanut, Maize, Rice, Sunflower seed, French bean and Apricot (1,24-26). Not all LTPs from plants are closely related. Mature Cherry LTP shows a great deal of identity with LTPs from Peach (88%) and Apricot (86%), but less with Maize (59%) (27). Similarly, Maize LTP was shown to cross-react completely with Rice and Peach LTP but not with Wheat or Barley LTP (1). Lipid transfer protein from Cowpea has a high homology of similarity to lipid transfer proteins of Maize (72%) (28). Rice non-specific lipid transfer protein has also been reported to closely resemble the structures of Wheat, Barley and Maize ns-LTPs (29).

A sensitisation rate of 47% among bakers with occupational asthma and of 35% among patients with grass pollen allergy, but without a clinical history of cereal allergy, was demonstrated to Tri a 25, a thioredoxin. Maize thioredoxin (Zea m 25) shares a 74% identity with Tri a 25, and exhibits distinct IgE cross-reactivity with its Wheat homologue. The study concluded that thioredoxins are cross-reactive allergens that might contribute to the symptoms of baker's asthma and might in addition be related to grass pollen allergy, and that therefore similar effects may be postulated for Zea m 25 (10). A more recent publication questioned whether this protein in Wheat is a true allergen, since it had been found that thioredoxin alleviates the allergic response and that there was no evidence that thioredoxin acted as an allergen (11).

A 16 kDa allergen, isolated and shown to be a Maize inhibitor of trypsin, was shown to cross-react completely with Grass, Wheat, Barley, and Rice trypsin inhibitors (1).

A Birch pollen protein with a mass of 35 kDa was isolated and shown to cross-react with 34 and 35 kDa proteins in Apple, Pear, Carrot, Banana and other exotic fruits. A high degree of sequence identity to isoflavone reductases (IFRs) and isoflavone reductase-like (IRL) proteins from several plants that also had a similar size was demonstrated, ranging from 56% for IFR from Pea and Chick pea and an IRL from Maize, to 80% for a Tobacco IRL. The authors postulated that this allergen may be responsible for less common pollen-related food allergies in patients allergic to Birch pollen (16).

The primary structure of the Japanese cypress (*Chamaecyparis obtusa*) allergen, Cha o 2, shows significant identity with the polygalacturonases of Avocado, Tomato, and Maize (30). The clinical implications of this finding have not been clarified yet.

In a study assessing the possible association of Oral allergy syndrome (OAS) with allergy to London plane tree (*Platanus acerifolia*), out of 720 patients evaluated, 61 (8.48%) were sensitised to *P. acerifolia* pollen. Food allergy was observed in 32 (52.45%) of the 61 patients, the allergens most frequently implicated being Hazel nut, Peach, Apple, Peanut, Maize, Chickpea and Lettuce. This study concluded that OAS in these patients may have been caused by primary respiratory sensitisation to Plane tree pollen. The authors suggest that profilin may be the responsible allergen (31).

Cross-allergenicity among 5 cereal grains, Rice, Wheat, Maize, Japanese millet (*Echinochloa crus-galli*) and Italian millet (*Setaria italica*), was examined by radioallergosorbent test and RAST inhibition assay. Significant close correlations between every combination of IgE antibody value for the 5 cereal grain extracts were found. A Rice protein of 16 kDa was shown to be one of the major allergens in Rice grain extracts (32).

Importantly, individuals with allergy to Maize pollen may also demonstrate allergy to Maize seed. In a group of 56 children with hay fever as a result of Maize pollen, more than half were sensitised to Maize seed allergens (33).

Clinical Experience

IgE-mediated reactions

Maize may moderately often sensitise or induce symptoms of food allergy in sensitised individuals (7,15,31,34-37). Allergic symptoms reported have included abdominal pain, nausea, vomiting, rhinitis, asthma, angioedema, atopic dermatitis, and anaphylaxis.

Latent sensitisation has often been described as a feature of Maize allergy. In 34 children with atopic dermatitis, 33 were SPT positive to Wheat and 18 to Oats. IgE antibodies to Wheat and Oats could be detected in 32 and 30 patients respectively. SPT to Rice, Maize, Millet or Buckwheat was positive in 16/34 patients (38-39). In 16 subjects with skin reactivity and the presence of IgE antibodies to Maize flour, only 6 complained of urticaria and/or other allergic symptoms following the ingestion of Maize-based foods. These patients developed symptoms following oral challenge with cooked Maize flour (polenta). The authors concluded that the presence of positive *in vivo* and *in vitro* tests to Maize flour had no clinical significance for most of the patients studied, and that food allergy to Maize has to be proven by DBPCFC studies. In these patients, a 50 kDa protein isolated was shown to be stable to cooking and digestion (15).

In a cross-sectional, descriptive, questionnaire-based survey conducted in Toulouse schools in France to determine the prevalence of food allergies among schoolchildren, of 192 questionnaires reporting a food allergy, of which 10 were excluded, the main foods reported as causing adverse reactions were Cow's milk (n=29), Egg (n=23), Kiwi (n=22), Peanut (n=20), Fish (n=19), Tree nuts (n=19), and Shrimp (n=13). Two individuals reported allergy to Maize (40).

Anaphylaxis to Maize protein has been reported (1,41). Anaphylaxis has even occurred during double-blind, placebo-controlled Maize challenges. (42) The Maize lipid transfer protein (Zea m 14) is reported to be responsible for this severe form of allergic reaction (5). Food-dependant exercise-induced anaphylaxis to Maize has also been described (43). In a study reporting on 7 cases of food-dependant exercise-induced anaphylaxis, responsible foods were Wheat (2 cases), Maize, Barley, Shrimp, Apple, Paprika and Mustard (44).

An unusual report was made of a 34-year-old carpenter who had previously been diagnosed with occupational asthma due to Rye flour added to wood boards. He developed severe anaphylaxis after testing a spoonful of baby cereal food – a non-Gluten, Rice and Corn formula. Skin reactivity and IgE antibodies were demonstrated for Wheat, Barley, Rye flour, Peanut and Mustard. A DBPCFC was positive for 0.1 g of the cereal. A 37 kDa protein band was demonstrated in the baby food, flours and Mustard. In addition, a well defined 23 kDa band was found in the Maize flour (45). The patient was specifically challenged with Maize alone.

Allergic reactions, including dermatitis, have been described with the Maize by-products Corn syrup, Corn dextrimaltose, Corn invert sugar, Corn isomerised dextrose and Corn D-psicose (46-48). Intravenous administration of a Maize-derived dextrose solution in a 23-year-old pregnant female patient at term gestation resulted in anaphylaxis. Symptoms included orofacial swelling, difficulty in breathing, hypotension, cardiac arrhythmia, voice hoarseness, total body warmth and flushing. These occurred within 8 minutes of initiation of a 5% dextrose Lactated Ringer's solution. Although the reaction elicited in this patient was unusual, clinicians should be aware of the possibility of Maize allergy due to the administration of IV fluids containing Maize-derived dextrose (49).

Patients allergic to Maize seed may also be allergic to Maize pollen, as Zea m 13 and homologous proteins are conserved plant allergens (4).

Occupational exposure to Maize, Maize flour, or Maize dust may result in occupational asthma or rhinitis, in particular in bakery workers, mill workers and those working in the animal feed industry (50). Whether atopy plays a dominant role or at most a minor role in the development of

grain dust-induced airway disease has not been fully evaluated yet. Occupational asthma to grain dust resulting in bronchoconstriction induced by an IgE-mediated reaction has been reported (17). Antigen-specific IgE, IgG and IgG4 antibodies to Maize dust in exposed workers have also been described (51). In a group of 35 men working in an animal food processing plant, the most frequent positive skin prick reactions occurred to the following occupational allergens: Fish flour (82.9%), Carotene (77.1%), Maize (65.7%), four-leaf clover (62.9%), Sunflower (54.3%), Chicken meat (31.4%), Soy (28.6%), and Yeast (22.7%) (52).

In 42 employees working in the animal feed industry, 15/42 (34.9%) had work-related respiratory dysfunction with or without nasal symptoms (53). In 32 Swine farmers, 37% were reported to be allergic to Maize flour (54).

Allergic reactions have also been reported to cornstarch powder used as a glove lubricant. Symptoms included urticaria, intermittent episodes of dyspnoea, oculorhinitis, angioedema, and asthma (55). Anaphylaxis to cornstarch glove powder has been described in 2 nurses. Both exhibited skin reactivity to cornstarch powder in water, with resultant anaphylaxis in 1. Both had negative *in vitro* and *in vivo* tests to Maize. Analysis of the cornstarch powder revealed only glucose and inorganic salts. The authors tentatively suspected that cornstarch, and not residual Maize proteins, was the responsible allergen (56).

Similarly, a 33-year-old nurse presented with persistent hand dermatitis. The IgE antibody levels were moderately raised for Latex, Avocado and Banana. Despite avoidance of latex gloves, she failed to improve. Repeated investigation demonstrated no skin reactivity for Latex, but a strong reaction to Maize, which was the powder (cornstarch) being used on the gloves (57). Furthermore, if Corn oil is not purified it may contain Maize protein.

Other reactions

Maize has been implicated as one of the causative foods of eosinophilic esophagitis, a disorder with symptoms suggestive of gastroesophageal reflux disease but unresponsive to conventional reflux therapies (58).

Contact urticaria and an anaphylactoid reaction from cornstarch surgical glove powder have also been described (59-60).

The dust of stored Maize has been reported as a cause of respiratory symptoms. During the storage process, Maize dust can be contaminated by moulds and thermophilic actinomycetes, which have not been described until now as causative antigens of these symptoms. Mould as a contaminant of Maize seed should be considered as a possible cause of hypersensitivity reactions to Maize (61). A study described occupational hypersensitivity pneumonitis in an agricultural worker who planted and stored Maize. Clinical findings, precipitating antibodies, and his improvement after avoidance of his work environment confirmed the diagnosis. *Aspergillus* species contaminating the Maize dust were probably the antigens that caused the disease (62).

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f7 Oat

Avena sativa

Family:	*Poaceae* (*Gramineae*)
Common names:	Oats, Oat, Oatmeal, Oat groats
Source material:	Untreated planting seeds
See also:	Cultivated oat g14

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Allergen Exposure

Geographical distribution

Oats, from an erect, tufted annual grass growing to 1.2 m, are of uncertain origin, but probably arose in Europe from 2 species, Wild oats (*A. fatua L.*) and Wild red oats (*A. sterilis L.*). Oats are now cultivated throughout the temperate zones of the world. The major growing areas are the USA, southern Canada, the USSR and Europe, particularly near the Mediterranean. Oats serve as food for humans, animal fodder and bedding, and - especially in the form of extracts - in a variety of industrial uses. There are many named varieties, with new forms being developed each year.

Environment

Oats are available as whole Oat grains when only the husks are removed; Oatmeal from cut or ground Oats; and rolled Oats when grains are cut in slices and then steamed and rolled. Oats are by far the most nutritious of the cereal grasses. They are high in vitamin B-1 and contain vitamins B-2 and E. Eaten as a cereal, they are probably best known as the breakfast cereal "porridge" or "oatmeal", but can also be used in many other ways. The seed can be sprouted and served in salads. The grain can be ground into flour and used in making biscuits, sourdough, etc. Oats are fairly low in gluten and so not suitable for making bread. Oat flour inhibits rancidity and, as an additive, increases the length of shelf-stability of fatty foods such as vegetable oils. Oats are also one of the basic ingredients of whisky. The roasted seed is a coffee substitute. Edible oil is obtained from the seed and used in the manufacture of breakfast cereals. Oats are often a major ingredient in cosmetics, creams and skin cleansers.

Oats are widely thought to have medicinal actions. Oat straw and the grain are prescribed to treat general debility and a wide range of nervous conditions.

Unexpected exposure

See under Environment.

Allergens

No allergens from this food have yet been characterised.

Allergens of 46 and 66 kDa have been isolated from Oats and have been classified as major IgE binding proteins in children with atopic dermatitis (1). The 66 kDa protein was found to bind to IgE antibodies in serum of 28 of 33 (84%) adult patients with atopic dermatitis. Non-specific binding to a region of this protein occurred, which the authors suggest may also represent lectin-like binding (2).

Oats has been shown to contain the panallergen profilin, but at very low levels compared to other foods, *e.g.*, a profilin IgE antibody level of 0.9 *vs*. 27.3 kU_A/l for Celery (3).

Three proteins of 25, 27 and 32 kDa have been identified, by immunoblotting using sera from patients with coeliac disease, as the major coeliac serum IgA-binding components of Oat endosperm. These corresponded to alpha 2, gamma 4, and gamma 3 avenins, respectively (4). These gluten-like allergens are in very low concentration in Oats, and recent studies have reported no adverse effect in patients with coeliac disease, even after long-term consumption of Oats.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus *Poaceae* could be expected (5). By RAST inhibition tests, cross-antigenicity was shown to exist among the cereal grains Rye, Wheat, Triticale, Barley, Oat, Maize and Rice. The degree of cross-reactivity closely paralleled taxonomic relationship and appeared to be in the following order of decreasing closeness: Wheat, Triticale, Rye, Barley, Oat, Rice and Maize. The allergenic activity in the Rye and Wheat extracts was found to be distributed among various fractions of different molecular weights (6). These results were supported by other studies reporting that in subjects sensitised to Wheat and Rye flour, there is significant cross-reactivity among the seed extracts of 12 cereals: Wheat, Durum Wheat, Triticale, Cereal rye, Barley, Rye grass, Oats, Canary grass, Rice, Maize, Sorghum and Johnson grass. Results of the study suggested that the bran layers of cereal grains are at least as allergenic as the flour (7). Sixteen proteins have been reported to be common among Wheat, Rye and Barley extracts, suggesting cross-reactivity among these cereals (2). However, in a study with challenges to the common cereals, 80% reacted to only 1 grain (8).

Wheat gliadin and the corresponding proteins of Rye, Barley and Oats were found to be the allergens in cereal-dependent exercise-induced anaphylaxis (9). Barley contains less gliadin than the other cereals.

A 51-year-old woman developed anaphylaxis following Millet ingestion; cross-reactivity to cereals could be demonstrated by positive SPT and/or IgE antibody measurements. However, these were not clinically relevant (10).

Cross-reactivity among Wheat, Rye, Barley, Oats, Maize, Rice, and the corresponding grass pollens has been reported (11).

Clinical Experience

IgE-mediated reactions

Oats may uncommonly induce symptoms of food allergy in sensitised individuals (12). Symptoms may include angioedema, urticaria, atopic dermatitis, asthma, rhinitis, and gastrointestinal symptoms such as nausea, vomiting and abdominal pain. Although IgE antibodies may be detected in patients, this may indicate only latent sensitisation (13-14).

On oral provocation studies in a group of children with cereal allergy, 18 exhibited a positive response to Wheat, 3 to Rye, 1 to Barley, and 1 to Oats. Symptoms involved the skin and the gastrointestinal and oropharyngeal regions. Onset was immediate in 8 children, delayed in 14, and both immediate and delayed in 1 (9).

Wheat gliadin and the corresponding ethanol-soluble proteins of taxonomically closely related cereals, including Oats, were found to be the allergens in cereal-dependent exercise-induced anaphylaxis. Five patients with positive SPT to a Wheat suspension had IgE antibodies to Wheat, Rye, Barley and Oats. The IgE antibodies were in particular directed against the ethanol-soluble protein fractions. The patients had been unaware of any cereal allergy, since anaphylaxis occurred only in association with exercise postprandially.

Oats may be a more relevant allergen in children with atopic dermatitis. In a study of 34 children with this condition, 33 were SPT positive to Wheat and 18 to Oats. IgE antibodies to Wheat was found in 32 children and in 30 to Oats (1). In a study evaluating topical treatments of atopic

dermatitis and the role of percutaneous sensitisation to Oats, it was concluded that Oat sensitisation in children with atopic dermatitis seen for allergy testing is higher than expected, and may have resulted from repeated applications of cosmetics with Oats on a predisposed impaired epidermal barrier (15). In a study evaluating the frequency of atopic dermatitis in an unselected German population and the role of food allergy in this condition, 27 selected patients were further evaluated, of whom 19 were shown to have skin reactivity to pollen and/or food allergens. Four were shown to have positive SPT to Oats (16).

Allergy to Oats may also result from occupational exposure, in particular in animal, bakery and mill workers. Baker's asthma has been reported (5).

Cough, wheezing, shortness of breath, fever, stuffy nose, and skin itching/rash on exposure to grain dust have been documented. The condition “grain fever” may also occur (17). Whether these symptoms result from antibody response or physical irritation has not been fully elucidated.

Other reactions

Allergic contact dermatitis to an *Avena* extract has been reported (18).

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe, cell-mediated gastrointestinal food hypersensitivity typically provoked by Cow's milk or Soy; it may also be provoked by Oats. Symptoms of typical FPIES are delayed and include vomiting, diarrhoea, lethargy and dehydration. Initial presentation may be severe, resulting in a suspicion of sepsis (19-20).

Oats were previously implicated as a cereal affecting individuals with coeliac disease. Recent studies have shown that the regular consumption of moderate amounts of Oats is safe and well tolerated by adults with coeliac disease and dermatitis herpetiformis (21). However, there are concerns that even if Oats themselves are safe, they nonetheless may be contaminated with Wheat, Rye, or Barley (22). Recent evidence suggests that oats that are pure and uncontaminated with other gluten-containing grains, if taken in limited quantities, are safe for most individuals with coeliac disease (23).

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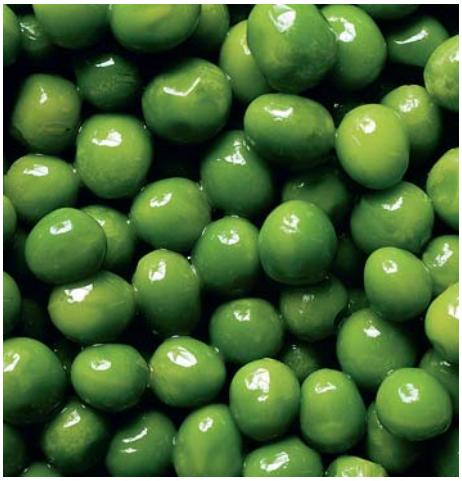
f12 Pea



Pisum sativum

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Pea, Common pea, Garden pea, Greenpea, Green pea, Dry pea. Snow pea, Sugar snap pea
Source material:	Dried peas
Synonym:	*P. humile*

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Allergen Exposure

Geographical distribution

Pea probably originated in south-western Asia, but it spread nearly throughout the world. Green peas are the number-one processed vegetable in the UK and the USA. The plant is an annual, dwarf or climbing, growing as high as 2 m. The Pea is a small, round, smooth or wrinkled seed, growing in pods.

There are many varieties of Pea, some grown to be eaten fresh, others to be used dried. (Dried Peas were the staple food of Europe during the Middle Ages.) Pod Peas are those that are eaten pod and all, namely the Snow pea and Sugar snap pea. Dried Peas are high in carbohydrate and fibre and low in fat, and an economical source of protein.

Environment

Green peas are marketed fresh, canned, or frozen. They can be cooked alone as a vegetable or added to other dishes. They can also be sprouted and added to salads, soups, etc. The mature seed may be dried and used whole or split (in which form it is often served as dhal), or ground into a powder and then used to enrich the protein content of flour. Roasted Peas can be a coffee substitute. The leaves and young shoots are cooked as a potherb. Peas, either whole or ground and extruded, are increasingly popular snack items.

Peas are reported to be contraceptive, fungistatic and spermacidal, and are said to have several other medicinal properties. The dried and powdered seed, for example, has been used as a poultice for skin complaints, including acne.

Allergens

Pea contains a number of allergens, of which a few have been characterised. In a study of 8 patients with adverse reactions after ingestion of foods from the legume family, IgE binding to a Pea 30-33 KDa protein region occurred in 7, and in 4 patients these were the major bands (1).

The following allergens from this plant have been characterised:

Pis s 1, a 44 kDa protein, a 7S vicilin-like globulin (2-5).

Pis s 2, a 63 kDa protein, a convicilin (4).

Pis s IFR, an isoflavone reductase (6-8).

Pis s profilin (9-10).

Two isoforms of Pis s 1, Pis s 1.0101 and Pis s 1.0102, have been characterised, and one of Pis s 2, Pis s 2.0101.

Immature Peas have low allergenicity compared to ripe Peas, as there are few storage albumin proteins at this stage. Allergens are expected to be found in the storage proteins. However, all levels of maturation of Green pea seeds show allergenicity and IgE-binding capacity, as do immature seeds, but total IgE-binding capacity rises with the progress of maturation.

The highest allergenic potency is caused by the albumin fraction, but globulin and glutelin fractions also contribute to the allergenicity of Green pea (11).

The globulin storage protein accounts for 75-80% of the total seed protein, and albumin the remainder. The amount depends on the cultivar. Skin reactivity has not been detected to globulin extracts, whereas albumin retained its allergenicity even when heated at 60 °C for 30 minutes or boiled at 100 °C for 5 minutes. Autoclaving at 120 °C for 15 minutes significantly reduced allergenic activity (12-13). Although some studies have shown no skin reactivity to the globulin protein, a protein belonging to the vicilin (7S globulin) family has been isolated and may yet be shown to have allergenic potential, as a vicilin from English walnut kernel (Jug r 2) has been shown to be a major allergen (14). Indeed, in a study of 3 patients with a history of anaphylaxis to Pea who subsequently had symptoms after ingestion of Peanut, immunoblotting studies demonstrated strong IgE binding, mainly to vicilin in Pea extract and exclusively to Ara h 1 in crude Peanut extract. IgE binding to Peanut could be inhibited by Pea but not or only partially the other way around (5).

A common feature of most legume allergens is their natural resistance to thermal, chemical, and, in some respects, proteolytic denaturation (15).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact is not seen frequently (16). In an *in vitro* study, the IgE antibody binding to protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked among the extracts of Peanut, Garden pea, Chick pea, and Soybean (17-18), and between Pea and Soybean (19). However, clinical studies have found that there is little cross-reactivity among members of the legume family (20-22).

Substantial clinical allergenic cross-reactivity exists among Lentil, Chick pea and Pea in the Mediterranean area, where these legumes are widely consumed, in contrast with the low clinical significance of legume cross-reactions (mainly between Peanut and Soybean) reported in the USA. Allergic reactions to Pea ingestion are frequently associated with Lentil allergy in the Spanish population. Vicilin and convicilin are potential major allergens from Pea seeds, and all of these proteins cross-react with the major Lentil allergen Len c 1, a vicillin (4).

In a study of Spanish children, evaluation of allergen-specific IgE demonstrated that most of the children were sensitised to more than 1 legume species. That a high degree of cross-reactivity existed among Lentil, Chick pea, Pea and Peanut was shown by inhibition studies. Thirty-nine patients were challenged with 2 or more legumes, and 32 (82%) reacted to 2 or more legumes: 43,5% to 3, 25,6% to 2, and 13% to 4 legumes. Seventy-three per cent of the patients challenged with Lentil and Pea had positive challenge to both, 69,4% to Lentil and Chick pea, 60% to Chick pea, and 64,3% to Lentil, Chick pea and Pea simultaneously. Peanut allergy was associated with allergy to Lentil, Chick pea and Pea, but less frequently. In this study, 82% of the children allergic to legumes were sensitised to pollen. Pea and Bean were the legumes with more *in vitro* cross-reactivity with *Lolium perenne*, *Olea europea* and *Betula alba*, probably as a result of common antigenic determinants or the coexistence of pollen and legume allergy. Panallergens as the cause seem to be less probable (23).

It is important to differentiate patients allergic to a legume from those only sensitised. This is demonstrated by a study of 8 patients with adverse reactions after ingestion of foods from the legume family. The majority had experienced symptoms with more than 1 legume (median 3 legumes), but sensitisation to other legumes without clinical symptoms also occurred (medium 5 legumes). Sensitisation and symptoms to 1 legume were observed only in 1 patient. IgE binding to a Pea 30-33 KDa protein region occurred in 7 out of 8 patients,

and in 4 patients these were the major bands. Serum IgE to Pea was <0.35 kU_A/l in 4 patients. For the Pea sensitised patients, immunoblotting assays with Chick pea and Bean detected numerous IgE binding proteins bands, but no predominant IgE binding pattern could be seen. This study thus demonstrated by *in vivo* and *in vitro* tests that most of the patients were sensitised to more than 1 food of the legume family (1).

In a Spanish study aimed at determining the prevalence of Lupin sensitisation in 1,160 subjects, using SPT evaluation, a 4,1% sensitisation rate (28 patients) was found, with a 75% co-sensitisation between Lupin and other legumes. Of the 28 patients, 7 were SPT positive to at least 1 legume: 9 to Fava bean, 8 to Soy, 13 to Chick pea, 8 to Pea, 12 to Peanut, 13 to Bean, 7 to Lentil (but 18 were not tested), 23 to at least 1 Pollen, 14 to grasses, 11 to Birch pollen, 15 to Mugwort, 10 to Olive and 8 to Latex (24).

An early study reported that the Ara h 1 from Peanut has significant homology of 60% to 65% with the vicilin seed storage protein found in Pea, and that there is homology of vicillin in most higher plants (25). In a more recent study of 3 patients with a history of anaphylaxis to Pea who subsequently had symptoms after ingestion of Peanut, immunoblotting revealed strong IgE binding, mainly to vicilin in Pea extract and exclusively to Ara h 1 in crude Peanut extract. Immunoblot and ELISA inhibition studies with crude extracts, as well as with purified proteins, showed that IgE binding to Peanut could be inhibited by Pea but not or only partially the other way around. Clinically relevant cross-reactivity between Pea and Peanut did not occur. Vicilin homologues in Pea and Peanut (Ara h 1) were thought to be the molecular basis for this cross-reactivity. (5) Tri f 1 from Fenugreek is a vicilin-like globulin and has been shown to be similar to vicilins from Soy, Pea, Bean, Lentil, Chick pea, and Lupin, which all cross-reacted serologically with the IgE antibodies from Peanut allergic patients (26).

Ana o 1 from Cashew has a 52-62% similarity to proteins found in African oil palm, Macadamia nut, Pea, Soybean and English walnut. These proteins have been variously described as vicilin-like protein pre-cursors, sucrose-binding proteins and precursors, and 7S globulins (27).

The Soybean glycinin G1 acidic chain shares IgE epitopes with Peanut Ara h 3. The glycinins in Ara h 3, Soybean, and Pea have a sequence similarity of 62% to 72% (28).

The isoflavone reductase allergen detected in Pea has a 56-80% sequence identity with IFR homologue proteins from various plants, *e.g.*, Birch, Apple, Pear, Orange, Mango, Litchi, Carrot, Banana, and Chick pea (7-8).

An association between grass pollinosis and sensitisation to Tomato, Potato, Pea, Peanut, Watermelon, Melon, Apple, Orange and Kiwi has been reported. A considerably high frequency of positive reactions to Tomato (39.2%), Peanut (22,5%), Pea (13.7%), and Wheat (11.7%) was observed in children with allergy to grass pollen (29-30).

Clinical Experience

IgE-mediated reactions

Legumes are among the most common foods causing allergic reactions in children and adults. Pea, a legume, may commonly induce symptoms of food allergy in sensitised individuals, and IgE antibodies to Pea have been detected in sensitised individuals (4,11,21, 31-34). Symptoms reported include atopic dermatitis, asthma, rhinitis, angioedema, dermatitis, oral pruritis, nausea, vomiting, and diarrhoea (1).

In a study of 8 Spanish patients with adverse reactions after ingestion of foods from the legume family, the majority experienced symptoms with more than 1 legume (median 3 legumes), but sensitisation to other legumes without clinical symptoms also occurred (medium 5 legumes). Sensitisation and symptoms to 1 legume were observed only in 1 patient. The symptoms were urticaria (4); oral allergy syndrome (2); anaphylaxis (1); angioedema (2) and asthma (1). Significantly, although

IgE binding to a Pea protein occurred in 7 out of 8 patients, and in 4 patients these were the major bands. Serum IgE antibodies to Pea were <0.35 KU_A/l in 4 patients. This study concluded that, according to *in vivo* and *in vitro* tests, most of these patients were sensitised to more than 1 food of the legume family (1). It is important, however, to differentiate patients allergic to a legume from those who are only sensitised. In the Mediterranean, where legume ingestion is high, clinical allergy is more common than in other Western countries such as the USA, where sensitisation may occur alone (4).

In this study in Delhi, the relevance of serum total and Pea-specific IgE were investigated in 216 asthmatics with food sensitisation. SPT was positive to Pea in 13 (35).

Food-induced anaphylaxis to Pea has been reported (36). Anaphylaxis to Pea has been reported in 3 patients who subsequently had symptoms after ingestion of Peanut. Although these patients were also affected by Peanut, clinically relevant cross-reactivity between Pea and Peanut did occur (5). Similarly, 5 patients with Peanut sensitivity had a history of adverse reactions to Pea (37).

A study reported on a 33-year-old woman who developed tongue swelling and burning and mouth itching minutes after eating baked beans. Similar symptoms occurred a day after ingesting Pea soup, and on another occasion within 15 minutes after eating a Bean burrito, and again 20 minutes after eating chilli containing Kidney and Pinto beans. SPT was positive to Red kidney and White bean but negative to Pea, Green and Lima beans. However, IgE antibodies were found to Pea, Red kidney, White and Pinto bean, and to Chick pea and Black-eyed pea (38).

In a study of 99 children with atopic dermatitis, Egg was the most common food allergen in children under 1 year of age. After that age, Apple, Carrot, Pea, and Soybean elicited positive reactions as often as Egg (39).

Pea has resulted in asthma following exposure to the cooking vapours (40). Occupational asthma has also been reported following exposure to Pea flour (41).

Other reactions

Infantile food protein-induced enterocolitis syndrome (FPIES) is a severe cell-mediated gastrointestinal food hypersensitivity typically provoked by Cow's milk and Soy. A study reported on other foods causing this syndrome: 14 infants with FPIES caused by grains (Rice, Oat, and Barley), vegetables (Sweet potato, Squash, String beans, Pea), or poultry (Chicken and Turkey) were identified. Typical symptoms of FPIES are delayed (median: 2 hours) and include vomiting, diarrhoea, and lethargy/dehydration. Eleven infants (78%) reacted to >1 food protein, including 7 (50%) who reacted to >1 grain. Nine (64%) of all patients with solid food FPIES also had Cow's milk and/or Soy FPIES. Initial presentation was severe in 79% of the patients, prompting sepsis evaluations (57%) and hospitalisation (64%) for dehydration or shock. None of the patients developed FPIES to maternally ingested foods while breastfeeding, unless the causal food was fed directly to the infant. (42) Similarly, 6 patients (4 males, 2 females, aged 3-12 months) were diagnosed with FPIES triggered by foods other than Cow's milk and Soy: Chicken in 4, Turkey in 2, Pea in 1, and Lentils in 1. (Five patients reacted to more than 1 food type.) All reactions developed within 2 hours of ingestion of the allergenic food (43).

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f13 Peanut

Arachis hypogaea

Family: *Fabaceae* (*Leguminosae*)

Common names: Peanut, Groundnut, Monkeynut

Source material: Shelled nuts

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Allergen Exposure

Geographical distribution

Peanuts were first cultivated in South America, as early as 3000 BC. Portuguese explorers transplanted Peanut plants to Africa, and from there they were carried by explorers to the rest of the world.

Peanuts are the seeds of an annual legume, which grows close to the ground and produces its fruit below the soil surface. This is in contrast to tree nuts like Walnuts and Almonds. Peanut is a member of the *Fabaceae* or legume family, whereas tree nuts are not. The Peanut plant is oval-leafed and about 45 cm tall. Delicate yellow flowers develop around the lower portion. The flowers pollinate themselves and then lose their petals as the fertilised ovary begins to enlarge. The budding ovary or "peg" grows down toward the soil. The Peanut embryo burrows into the soil surface and begins to mature, taking the form of the Peanut.

Multiple Peanut varieties are grown in the USA, with more than 40% of the American Peanut crop consumed as Peanut butter (1). Runners have become the dominant Peanut type grown in the U.S. due to the spectacular increase in yield that they allow; they are a very important source of Peanut butter. Virginias have the largest kernels and account for most of the Peanuts roasted and sold in their shells. Spanish peanuts have smaller kernels covered with a reddish-brown skin. They are used predominantly in Peanut candy, but with significant quantities also used for salted nuts and Peanut butter. They have higher oil content than the other types of Peanuts, which is advantageous for oil extraction. Valencias are small, very sweet Peanuts usually roasted and sold in the shell, or boiled, but seldom used in processed foods.

Environment

Peanuts are consumed mainly as Peanut butter, as snacks (roasted, salted, plain or dry roasted), in candy and in baked goods. Peanuts also yield widely used cooking oils (both refined and crude, aromatic and non-aromatic). In China, Peanut is second only to Soy as a source of fat and oil. Peanut flour is an important ingredient in a variety of processed foods. The American George Washington Carver developed more than 300 uses for Peanuts, some of them industrial rather than culinary.

Peanut oil is the refined fixed oil obtained from the seed kernels. Hydrogenated Peanut oil, Peanut acid, and Peanut glycerides are

all derived from Peanut oil. The oils and glycerides are skin-conditioning agents in cosmetics. The acid functions as a surfactant or cleansing agent, and the flour is an abrasive, bulking agent and/or viscosity-increasing agent. Peanut oil, if not highly purified (and cold-pressed or extruded oils tend not to be), may contain Peanut allergen (2-4). Some Peanut-allergic patients react to crude Peanut oil but not refined Peanut oil (5). The quality of Peanut oil in chocolate, for example, may be crucial in determining whether or not allergic reactions occur. Peanut oil has been used to manufacture infant food, resulting in sensitisation in some children as a result of the presence of Peanut allergens (6-7). Creams and ointments containing Peanut oil may lead to sensitisation; oily solution vitamin preparations are an example (8-9).

Peanut flour is made from raw Peanuts that have been cleaned, blanched, roasted and processed to produce a lower-fat Peanut flour with a strong roasted Peanut flavour. Peanut flour is used in confectionery, seasoning blends, bakery mixes, frostings, fillings, and health-food bars (10).

Peanuts have been deflavoured, reflavoured and sold as Walnuts, Almonds, and Pecan nuts (11).

Unexpected exposure

See under Environment.

Allergens

Peanut contains up to 32 different proteins, of which at least 18 have been identified as being capable of binding specific IgE (12-13). Varieties of Peanuts from different parts of the world contain similar proteins, including Ara h I and Ara h 2, and the IgE-binding properties have also been reported to be similar to a great extent (14).

The major Peanut allergens are homologous to the seed storage proteins of the conglutin, vicilin, and glycinin families (15).

Peanut proteins were originally classified as albumins (water-soluble) or globulins (saline-soluble); the globulins were in turn subdivided into arachin and conarachin fractions (the major storage proteins). There are 2 polymorphic forms of arachin, A and B. Conarachin can be separated by ultra-centrifugation into 7.8 S and 12.6 S components. The latter component is designated as conarachin II or alpha conarachin. Other components of the albumin fraction of Peanuts are agglutinins, lectin-reactive glycoproteins, protease inhibitors, alpha-amylase inhibitors and phospholipases (16).

The major storage proteins of legumes are globulins, subdivided into legumins and vicillins. The 2 major Peanut allergens, Ara h 1 and Ara h 2, are heat-stable vicillin proteins (17).

A number of allergens have been characterised to date:

Ara h 1, a 63.5 kDa - 65 kDa protein, a heat-stable major allergen, and a vicilin seed storage protein (17-37). Ara h 1 also contains a carbohydrate moiety (38).

Ara h 2, a 17.5 kDa protein, a major allergen, a conglutin seed storage protein and a trypsin inhibitor (18,21,24,26,28, 34,37,39,40-52). The isoforms Ara h 2.0101 and Ara h 2.0201 have been isolated (53-54).

Ara h 3, a 60 kDa protein, a major allergen, and an 11S globulin (glycinin-like) seed storage protein (21,26,33,37,55-62). Ara h 3 may also function as a trypsin inhibitor (63-64).

Ara h 4, a glycinin seed storage protein (24,28,33). Ara h 4 and Ara h 3 are considered to be the same allergen (57).

Ara h 5, a 15 kDa protein, and a profilin (24,65-66).

Ara h 6, a 2S albumin, a heat- and digestion-stable protein (24,26,28,48,51-52,67-68).

Ara h 7, a 2S albumin (24,28).

Ara h 8, a 16.9 kDa protein, a Bet v 1-homologous allergen (28,69-71).

Ara h 9, a lipid transfer protein (37,72-73).

Ara h Oleosin, a 18 kDa protein (74).

Ara h Agglutinin (75-76).

Recombinant proteins include:

rAra h 1 (77-78).

rAra h 2 (79).

Ara h 3 (57).

Ara h 4 (80).

Ara h 5 (66).

rAra h 6 (67).

rAra h 8 (70).

Ara h 1 comprises 12% to 16% of the total protein in Peanut. It has a stable trimeric structure that protects IgE binding epitopes from degradation (21,81). In a study where native Ara h 1 from Peanuts was purified using only size exclusion chromatography, the allergen appeared to exist in an oligomeric structure rather than a trimeric structure. As structural characteristics are important for a protein's allergenicity, this may imply a different allergenicity for Ara h 1 than previously described (29).

At least 23 different linear IgE-binding epitopes, located throughout the length of the Ara h 1 protein, have been identified (18). Ara h 1 and Ara h 2 are recognised by 70-90% of patients with Peanut allergy (82-83). However, some subjects fail to bind to either Ara h 1 or Ara h 2 (84). But this may vary among populations: in population studies, Ara h 1 was recognised by over 95% of patients from a North American population (17), whereas the same allergen was recognised by only 35% (19), 65% (24) and 70% (82) of patients of 3 European populations. These differences in recognition were not found for Ara h 2 (14). In some population groups, Ara h 2 may be the more prevalent allergen, and previously unidentified Peanut proteins with molecular weights somewhat lower than 15 kDa may be important allergens as well (85).

Although the major allergens are heat-stable and resist gastric acid fluid degradation, and Ara h 2 subjected to roasting has been shown to protect Ara h 1 from proteolytic digestion when co-incubated (39), the allergenicity of Peanut allergens has been clearly shown to be dependant on the degree of heat the substance is exposed to, and it is evident that roasting increases the allergenicity of Peanuts (90,86-88). For example, the prevalence of Peanut allergy in China is much lower than in the West. The methods of frying or boiling Peanuts practiced in China were shown to result in less allergenicity, compared with the method of dry roasting practiced widely in the United States. Roasting uses higher temperatures (150-170 °C) than boiling (100 °C) or frying (120 °C). This may help explain the difference in prevalence of Peanut allergy observed in the 2 countries. Compared with the amount in roasted Peanuts, the amount of Ara h 1 was reduced in the fried and boiled preparations, resulting in a significant reduction of IgE-binding intensity. There was significantly less IgE binding to Ara h 2 and Ara h 3 in fried and boiled Peanuts, compared with that in roasted Peanuts, even though the protein amounts were similar in all 3 preparations (89). The decrease in allergenicity of boiled compared to roasted Peanut may result mainly from a transfer of low-molecular-weight allergens into the water during cooking (32).

Although native Ara h 1 undergoes a significant heat-induced denaturation on a molecular level, the allergenicity of Ara h 1 is unaffected by heating, indicating that the recognition of conformational epitopes of Ara h 1 by IgE either is not a dominant mechanism or is restricted to parts of the protein that are not sensitive to heat denaturation (23). Other studies have reported that the protein modifications made by the Maillard reaction contribute to this effect (90- 91).

Furthermore, mature roasted Peanuts have been shown to exhibit a higher IgE binding and advanced glycation end adducts level than immature roasted Peanuts (91-92).

Other factors may also be involved: for example, the protein concentration is higher in raw Peanuts (approx 16.6 g per 100 g) than in roasted Peanuts (approx 2.6 g per 100 g), and the increased histamine content may have some influence (93). Ara h 1 levels are up to 22-fold higher in oven-roasted than in raw Peanuts (820 *vs.* 37 µg/ml) (31).

Saliva has been shown to contain up to 1,110 mg/ml Ara h 1, and therefore, as calculated through extrapolation, a single kiss could transfer up to 88.8 mg of Peanut proteins in saliva (94).

In the case of Ara h 2, a protein that functions as a trypsin inhibitor, it was shown that roasting caused a 3.6-fold increase in trypsin inhibitory activity. Functional and structural comparison of the Ara h 2 purified from roasted Peanuts to native and reduced Ara h 2 from raw Peanuts revealed that the roasted Ara h 2 mimics the behaviour of native Ara h 2 in a partially reduced manner (39).

Ara h 2 consists of 2 isoforms, namely Ara h 2.0101 and Ara h 2.0201. Ara h 2.0201 has similar but higher IgE binding than the originally sequenced Ara h 2.0101 isoform (81% *vs*. 77%) and contains other IgE specificities (53). Of the 2 Ara h 2 isoforms, Ara h 2.02 might be the more potent allergen (54). Ara h 2 was found to be a much more potent allergen than Ara h 1 (95). The 2S albumin Ara h 2 is homologous with the minor allergen Ara h 6. Native Ara h 2 and Ara h 6 have virtually identical allergenic potency. The extreme immunological stability of the core structures of Ara h 2 and Ara h 6 provides an explanation for the persistence of the allergenic potency even after food processing (48).

Children with Peanut allergy recognise mainly Ara h2 and Ara h6, and this recognition remains stable over time. In Peanut-allergic adults, IgE is mainly directed to Ara h1 and Ara h2 (51).

Ara h 1, Ara h 2, and Ara h 3 are considered to represent >30% of the total protein content of Peanut (96).

Ara h 3 was in the first instance identified as a 14 kDa protein, but cloning of its gene revealed a protein of approximately 60 kDa (55,57,64). Ara h 3 is recognised by serum IgE antibodies from 45% - 50% of patients with Peanut sensitivity (64,97). Ara h 3 consists of a series of polypeptides ranging from approximately 14 to 45 kDa that can be classified as acidic and basic subunits; this is similar to the subunit organisation of Soy glycinin (57). Various levels of the 3 major Peanut allergen genes, Ara h 1, Ara h 2 and Ara h 3, and of their corresponding proteins, have been found in all Peanut cultivars. However, Ara h 3 expression patterns among cultivars are more variable than patterns of Ara h 1 and Ara h 2. Transcripts were tissue-specific, observed in seeds but not in leaves, flowers, or roots, and were undetectable during seed germination (98). In a study, 60 accessions in the U.S. Peanut core collection were analysed, along with 88 Florida Peanut breeding program lines. An accession from India had the lowest level of Ara h 1 (7.0%). An accession from Nigeria had the highest level of Ara h 1 (18.5%), but the lowest level of Ara h 2 (6.2%). An accession from Zambia had the highest level of Ara h 2 (13.2%), but the lowest level of Ara h 3 (21.8%). Two accessions, 20 lines, and 2 Peanut cultivars (Florunner and Georgia Red) contained little or no trace of a 36 kDa Ara h 3 isoform, Ara h 3-im (99).

Although Ara h 3 is regarded as a minor allergen, in a study of a group of Peanut-allergic Italian children, it was found that they were specifically sensitised to the basic subunit of Ara h 3 (62).

Ara h 5 shows up to 80% amino acid sequence identity with the panallergen profilin, but Ara h 5 is present only in low amounts in Peanut extracts (66); 13% to 16% of Peanut-allergic individuals are sensitised to Peanut profilin (65-66).

Ara h 6, which has structural similarities to Ara h 2, also has equal *in vitro* and *in vivo* potency (95). Ara h 6 has been reported to be a minor allergen. However, in a study of 29 Peanut-allergic patients, Ara h 6 was recognised by 20. Ara h 6 has homology to Ara h 2, especially in the middle part and at the C-terminal part of the protein; and almost complete inhibition of IgE-Ara h 6 by Ara h 2 demonstrates that at least part of the epitopes of Ara h 6 are cross-reactive with epitopes on Ara h 2; furthermore, Peanut-allergic patients recognise Ara h 6 both *in vitro* and *in vivo* to a similar extent as in the case of Ara h 2. Researchers have therefore concluded that Ara h 6 should be considered a major Peanut allergen as well (52).

Compared with Ara h 6, Ara h 2 appears to be the more potent allergen, even though the 2 Peanut allergens share substantial cross-reactivity. Both allergens contain cores that are highly resistant to proteolytic digestion and to temperatures of up to 100 °C. The reduction in IgE antibody-binding capacity does not necessarily translate into reduced allergenic potency, and native Ara h 2 and Ara h 6 have virtually identical allergenic potency, compared with the allergens that were treated with digestive enzymes. The folds of the allergenic cores are virtually identical with each other and with the folds of the corresponding regions in the undigested proteins. The extreme immunological stability of the core structures of Ara h 2 and Ara h 6 provides an explanation for the persistence of the allergenic potency even after food processing (48).

In a study of recombinant Ara h 6, the presence of allergen-specific IgE to Ara h 6 was strongly associated with patients having symptoms of anaphylaxis and urticaria, but not with patients having isolated oral allergy syndrome. This may be an indication that Ara h 6 is a candidate for association with severe clinical reactions (100).

As mentioned above, children with Peanut allergy recognise predominantly Ara h2 and Ara h6, which remains stable over time. In Peanut-allergic adults, IgE antibodies are mainly directed to Ara h 1 and Ara h 2. A role for Ara h 6 in diagnosis has been proposed. In contrast to adults, IgE in children can fluctuate over time, indicating that children may have a more dynamic reactivity to Peanut. In a study that examined the IgE reactivity to major Peanut allergens in Peanut-allergic children at 2 points in time, 20 Dutch children (3-15 years old) with Peanut allergy DBPCFC were evaluated. Before DBPCFC, all Peanut-allergic children showed IgE reactivity to recombinant Ara h 2; Ara h 6 was recognised by 16 children, and Ara h 1 and Ara h 3 by 10 children. After 20 months, Peanut-specific IgE levels (median 23 kU_A/l) and the individual recognition of major allergens were comparable with the levels and recognition before challenge (median 28.2 kU_A/l). SPT with Ara h 2 and Ara h 6 was positive in most children, whereas SPT for Ara h 1 and Ara h 3 was positive in approximately half of the children. Ara h 6 induced the largest wheals. Therefore, Ara h 2 and Ara h 6 were the most frequently recognised major Peanut allergens in children (101).

Ara h 8 has a low stability to roasting and no stability to gastric digestion. rAra h 8 inhibited IgE binding to Peanut in 4 of 7 tested patient sera (70).

In a study of sera from 12 patients with atopic dermatitis and a positive DBPCFC to Peanut, Peanut agglutinin bound IgE in only 50% of the sera (75). Although Peanut agglutinin is considered in the literature to be a minor allergen, a study reported that the majority of sera from Peanut-sensitive patients showed a high level of IgE binding to the lectin even after heat treatment; and that, contrary to published data, non-enzymatic browning reactions seemed to deteriorate the IgE affinity of the lectin (102).

Nonetheless, individuals are sensitised to a number of allergens in a heterogeneous way, rather than stereotypically to only 1 or 2. For example, in an examination of sera of 40 Peanut-allergic patients, 14 individual recognition patterns and the following frequency of allergen-specific IgE binding emerged: Ara h 1 was recognised by 65%, Ara h 2 by 85%, Ara h 4 by 53%, Ara h 5 by 13%, Ara h 6 by 38% and Ara h 7 by 43% of the sera (24).

Similarly, in a study of 30 Peanut-allergic individuals, the majority of patients with a positive SPT were sensitised to Ara h 2 (25/30, 83%) and Ara h 6 (26/30, 87%). Sixteen patients (53%) were sensitised to Ara h 1 and 15 patients (50%) to Ara h 3. All patients with a positive SPT to Ara h 1 and/or Ara h 3 were also sensitised to Ara h 2 and/or Ara h 6. The eliciting dose for subjective reactions varied from 0.1 mg up to 300 mg Peanut, and from 10 to 3,000 mg for objective symptoms (95).

Furthermore, a number of uncharacterised allergens have been detected in Peanut. A Peanut agglutinin has been isolated, and bound IgE in 50% of the Peanut challenge-positive patients (75). An oleosin, a member of a family of proteins involved in the formation of oil bodies, has been isolated

and found to bind with 3 of 14 sera of Peanut-allergic patients (74). Hybridisation may have no effect on the allergenicity of Peanut: high-oleic Peanuts, known as the SunOleic type, show no difference in allergenicity (88). Similarly, no difference in the allergic components of either raw or roasted extracts of Korean or American Peanuts could be demonstrated (103).

Two different genes encoding class II chitinases have been isolated from Peanut, suggesting that stress to the plant can result in the formation of a chitinase protein (104). The clinical relevance of either gene has not been determined. Similarly, during Peanut maturation and curing, a new class of proteins, namely stress proteins or dehydrin-like proteins, is produced (105).

Peanut allergens have been shown to cross into breast milk and may sensitise infants. In a study of 23 lactating women given 50 g of Peanut to eat, Peanut protein was detected in the breast milk of 11. It was detected in 10 subjects within 2 hours of ingestion and in 1 subject within 6 hours. The median peak Peanut protein concentration in breast milk was 200 ng/ml (range, 120-430 ng/ml). Both major Peanut allergens, Ara h 1 and Ara h 2, were detected (106). Indeed, Peanut proteins can be found in breast milk for several hours after a mother has eaten Peanuts (107).

Although sensitisation to Ara h 1 and Ara h 2 occurs in the great majority of Peanut-allergic individuals, the wide range of allergens present in whole Peanut protein extract appears to be most appropriate to consider when testing for Peanut allergy (84).

However, appreciating the involvement of individual Peanut allergens may enable better diagnosis and better assessment of severity and prognosis, and may aid immunotherapy.

For example, a Dutch study investigated whether sensitisation to the individual allergens Ara h 1, Ara h 2, Ara h 3 and Ara h 6 correlated with clinical severity. The reactivity of purified Peanut allergens was measured by SPT and by IgE immunoblot in 30 patients. The majority of patients recognised Ara h 2 and Ara h 6. Patients with severe symptoms had a higher skin reactivity to Ara h 2 and Ara h 6 at low concentrations and to Ara h 1 and Ara h 3 at higher concentrations, compared with patients who had mild symptoms. Patients with severe symptoms also recognised a greater number of allergens and showed a higher cumulative SPT response, compared with patients with mild symptoms. No significant differences were observed between patients with a low ED and patients with a high ED. Therefore, Ara h 2 and Ara h 6 appeared to be more potent than Ara h 1 and Ara h 3. Skin reactivity both to low concentrations of Ara h 2 and Ara h 6, and to higher concentrations of Ara h 1 and Ara h 3, was shown to be indicative of severe symptoms (95). However, in a similar study conducted in the UK to evaluate whether the pattern of IgE binding to specific Peanut allergens is associated with the severity of clinical symptoms, the results demonstrated that the promiscuity of IgE binding appeared more important than the recognition of individual proteins (36).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the *Fabaceae* (*Leguminosae*) could be expected but in fact does not occur frequently (108). Moreover, the taxonomic classification of Peanut and tree nuts does not appear to predict allergenic cross-reactivity (109).

Although Peanut shares homologous proteins with other beans and legumes, and although several studies have demonstrated that individuals with clinical reactions to a single legume often (38 to 79%) show the presence of IgE sensitisation in SPT and allergen-specific IgE tests to a variety of legumes, the majority do not show clinical reactions to the other legumes (110-112). Further evidence indicates that although one would expect Peanut-allergic individuals to have a high risk of cross- or co-reactivity to Soya bean, a family member, blinded food challenges have shown a low rate (109).

Similarly, in a study reporting on reactivity of the sera of Peanut-allergic subjects to 11 different legumes, as shown by *in vitro* tests, cross-allergenicity was demonstrated to be most marked among the

extracts of Peanut, Garden pea, Chick pea, and Soybean; yet clinical studies found little cross-reactivity among members of the legume family (109). In a study of 60 children with Peanut allergy who were evaluated for allergy to Soy and other legumes (Pea, String bean, Lima bean) by blinded food challenges, 6.5% of those with severe Peanut allergy had reactions to Soy. Overall, only 2 of 41 (5%) with any 1 positive challenge reacted to more than 1 legume. Up to 15% of Peanut-allergic patients may react to other members of the legume family (113). Furthermore, other legumes rarely provoke severe anaphylactic reactions or result in a lifelong allergy (114).

However, patients with Soya bean allergy mainly mediated by cross-reactivity to Birch pollen allergens have been recently described; a majority of whom were reported to have Peanut allergy. Of 9 Swiss and 11 Dutch patients with Peanut and Birch pollen allergy and a positive double-blind, placebo-controlled food challenge result to Peanut, all experienced symptoms in the oral cavity, progressing to more severe symptoms in 40% of patients. Recombinant Ara h 8-specific IgE was demonstrated in 85%, and IgE binding to Ara h 8 was inhibited by Bet v 1 in inhibition studies. In EAST inhibition, recombinant Ara h 8 inhibited IgE binding to Peanut in 4 of 7 tested patient sera. The study concludes that Peanut allergy might be mediated in a subgroup of the patients by means of cross-reaction of Bet v 1 with the homologous Peanut allergen Ara h 8. The study also demonstrated a low stability of Ara h 8 to roasting and no stability to gastric digestion. Basophil histamine release with rAra h 8 was demonstrated in 5 of 7 tested sera (70).

Lupin, which is not a common food in some parts of the world (*e.g.* USA), is a legume that appears to have a high degree of cross-reactivity with Peanut. In a French study, 11 of 24 Peanut-allergic individuals were shown to have skin reactivity to Lupin flour. Double blind oral challenges with Peanut and Lupin flour performed in 8 of the 24 patients were positive in 7 when the same dose of both was used. The major Lupin flour allergen (a 43 kDa protein) is present in Peanuts. The risk of cross Peanut-Lupin allergy was reported to be high, in contrast to the risk with other legumes. The authors suggested that the inclusion of 10% Lupin flour in Wheat flour without mandatory labelling makes Lupin a hidden allergen, presenting a major risk of cross-reaction in subjects already allergic to Peanut products (115). Further confirmation of the high risk of cross-reactivity between Lupin and Peanut is documented by a case of Peanut cross-allergy to Lupin flour in hot dog bread (116); there is also reported to be an increased risk of serious acute asthma due to Lupin flour, a risk associated with Peanut allergy (117).

Reactivity to tree nuts is a serious problem for Peanut-allergic people. Peanut and tree nut allergic reactions coexist in 25-50% of Peanut-allergic patients, and allergic reaction to tree nuts such as Walnuts, Cashews, Pecans and Pistachios can develop even though tree nuts are from a different botanical family (118-120). Reactions frequently occur on first known exposure and may be life-threatening. It is unclear whether this is due to genuine cross-reactivity or to the coexistence of separate allergies in broadly atopic individuals. Patterns of reported co-sensitisation vary among studies. In 60 adult Peanut-allergic individuals, 40 (66%) reported allergy to tree nuts, but 50 (83%) had a positive SPT to 1 or more tree nuts (5). The relative frequency of allergy to individual tree nuts concomitant with Peanut allergies is reported to reflect the consumption of various types of nuts by the general population: Almond, Hazel and Brazil nuts are implicated far more commonly than Pecan, Cashew and Pistachio (164).

Of course, cross-reactivity can be calculated from the other direction. For example, 5 of 12 Brazil nut-allergic individuals were also allergic to Peanut (121).

Ara h 1 has a high sequence similarity with other plant vicilins, members of the cupin superfamily (122). However, although there are significant areas of homology between Ara h 1 and Soy vicillins, these areas do not appear to be significantly involved in the binding of IgE antibodies, which may account for the low frequency of co-existent

Peanut and Soy allergy, despite the frequency of positive SPT to Soy (55,78). Similarly, even though Jug r 2, the allergen from Walnut, exhibited significant homology to the vicilin group of seed proteins, including those in Cocoa bean (*Theobroma cacao*) and Cottonseed (*Gossypium hirsutum*), there is minimal or no cross-reactivity between Jug r 2 and Pea vicilin, Peanut proteins, or Cacao proteins (123). Nonetheless, this may not be completely clear-cut, as demonstrated by a report on 3 patients with a history of anaphylaxis to Pea who subsequently had symptoms after ingestion of Peanut. Peanut-related symptoms consisted of oral symptoms in all patients, with additional urticaria and dyspnoea or angioedema in 2 patients. All patients had a positive skin prick test response and an increased IgE antibody level to Pea and Peanut. Immunoblotting revealed strong IgE binding, mainly to vicilin in Pea extract and exclusively to Ara h 1 in crude Peanut extract. IgE binding to Peanut could be inhibited by Pea but not, or only partially, the other way around. Clinically relevant cross-reactivity between Pea and Peanut does occur and is attributable to vicilin homologues (124).

The major Peanut allergen Ara h 2 shares IgE-binding epitopes with Almond and Brazil nut allergens, which may contribute to the high incidence of tree nut sensitisation in Peanut-allergic individuals (125). However, an earlier study reported that conformational analysis of the linear IgE-binding epitopes mapped on the molecular surface of Ara h 2 showed no structural homology with the corresponding regions of Walnut Jug r 1, Pecan Car i 1 or Brazil nut Ber e 1; it was inferred that the absence of epitopic community does not confirm the allergenic cross-reactivity observed between Peanut and Walnut or Brazil nut, which presumably depends on other ubiquitous seed storage protein allergens, namely the vicilins. However, the major IgE-binding epitope identified on the molecular surface of the Walnut Jug r 1 allergen shared a pronounced structural homology with the corresponding region of the Pecan nut Car i 1 allergen. With the exception of Peanut, 2S albumins could thus account for the IgE-binding cross-reactivity observed among some other nuts, *e.g.*, Walnut and Pecan nut (49).

Ara h 3, an 11S globulin seed storage protein family member, may result in cross-reactivity between Peanut other foods containing other such family members, including Hazel nut and Soya bean. Homology among these 3 proteins ranges from 45% to 50%. One IgE binding epitope of Ara h 3 has a 67% homology of amino acid residues with the corresponding area of Cor a 9 of Hazel nut (56).

Ara h 5 shows up to 80% amino acid sequence identity with the panallergen profilin, but this allergen is present only in low amounts in Peanut extracts. Immunoblot analysis of 50 sera from individuals sensitised to Peanut showed that 16% had mounted a detectable IgE response to the newly identified Peanut profilin, which indicates some risk for cross-reactivity with other profilin-containing foods and plants (66).

Ara h 8 also has cross-reactive potential. Examination of the sera of 5 patients in relation to 4 recombinant allergens led to the conclusion that IgE cross-reactivity existed between Bet v 1 and its homologues Gly m 4 from Soybean, Ara h 8, and Pru av 1 from Cherry. On all 4 proteins, 1 IgE-binding surface area that was recognised by all patients, and 2 that were recognised by 3 patients, were identified (126). Lupin is an emerging cause of food allergy because of recent large-scale introduction into processed foods and frequent cross-reactions with other members of the legume family. Sequence comparison and modelling demonstrated highly significant sequence homology and molecular similarity between the allergen Ara h 8 of Peanut and the pathogenesis-related protein PR-10 of White lupin. (Another protein of Lupine the beta-conglutin precursor, was found to be significantly homologous to the Ara h 1 allergen of Peanut) (127).

In a study, approximately a third of patients sensitised to grass pollen were found, in IgEantibody investigations, to have significant serum levels of anti-Peanut IgE,

without positive Peanut skin reactivity and without Peanut-related allergic symptoms. This was attributed to the presence of cross-reactive carbohydrate determinants (CCD) of glycoproteins. In a study investigating the biologic activity of IgE directed to CCD, cross-reactive IgE directed to carbohydrate determinants of glycoproteins, as found in grass pollen-sensitised patients, was shown to have poor biologic activity, therefore causing positive IgE antibody results without apparent clinical significance (38).

Clinical Experience

IgE-mediated reactions

Peanuts are a significant cause of serious food allergy in both adults and children. Unlike other food allergies, Peanut allergy usually begins in childhood and persists throughout the affected individual's lifetime. Only approximately 20% of young children will develop tolerance (111,128). More precisely, Peanut allergy persists in about 80% of young children reacting to Peanut in the first 2 years of life, and virtually all individuals reacting to Peanut beyond the age of 5 years (129). Approximately 75% of children experience a reaction with their first known Peanut exposure suggesting, early sensitisation (119,130-131). Peanut allergic reactions are more likely to be severe or even fatal than reactions to other food allergens (13).

Atopic dermatitis, angioedema, asthma, diarrhoea, nausea and vomiting, and anaphylaxis have been reported. Urticaria may be a prominent symptom (132). Angioedema of the lips and tongue following ingestion of Peanut butter, and localised urticarial reactions following direct skin contact, were described (133). A patient with a history of a burning tongue, together with discomfort of the labial and buccal mucosae, improved after Peanut was removed from her diet (134). Severe reactions may be associated with abdominal pain at the onset of the response (17,43). In one study, the commonest symptom was facial angioedema, and the major feature accounting for life-threatening reactions was laryngeal oedema (118). Food-dependant exercise-induced anaphylaxis has been described (135-137). A study reported a high frequency (50%) of food hypersensitivity in patients with allergic rhinoconjunctivitis; Peanut was one of the most frequent food allergens encountered (138). A significant association was reported to exist between recurrent serous otitis media and food allergy in 81 of 104 patients. An elimination diet resulted in a significant amelioration of the disease in 86% of the patients, and a challenge diet provoked recurrence of symptoms in 94%. The most prevalent allergens involved were Cow's milk, Wheat, Hen's egg, Peanut, Soy and Corn (139).

Although not reported frequently, asthma may be a significant feature in Peanut allergy. In a French study evaluating 163 asthmatic children with food allergy, and exploring food-induced asthma via double-blind placebo controlled food challenges, the most frequent offending foods were found to be (sometimes in association) Peanut (30.6%), Hen's egg (23.1%), Cow's milk (9.3%), Mustard (6.9%), Codfish (6%), Shrimp (4.5%), Kiwi fruit (3.6%), Hazel nut (2.7%), Cashew nut (2.1%), Almond (1.5%), and Garlic (1.2%) (140). Asthma caused by Peanuts in a 3-year-old child was established by chance, and strict avoidance of Peanut led to complete remission of symptoms and rapid termination of inhalation therapy. The authors suggested that as severe Peanut allergy in asthmatic infants carries a risk of anaphylaxis, it is useful to look for Peanut allergy in all infants with severe asthma (141).

Food allergy affects 6-8% of children < 4 years of age in the USA, and 2% of the population >10 years of age. It is the leading cause of anaphylaxis treated in hospital casualty departments (113). Food allergy accounts for about 30,000 anaphylactic reactions, 2,000 hospitalisations and 200 deaths each year in the USA (142). Allergy to Peanuts and tree nuts accounts for the majority of fatal and near-fatal anaphylactic reactions (143-144). About a third of Peanut-sensitive patients have severe reactions to Peanuts. As little as 100 micrograms of Peanut protein provoke symptoms in some subjects with Peanut allergy. Asthmatics with Peanut sensitivity appear more likely to develop fatal reactions,

and this is thought to be because of the exquisite sensitivity that asthmatics have to the chemical mediators of anaphylaxis. Severe reactions may occur within a few minutes of ingestion. Peanut may in particular affect children with chronic severe asthma. In a double-blind food challenge of 38 children, Peanut resulted in adverse reactions, which were chiefly gastro-intestinal, even though asthma was the common presenting complaint (145).

In the USA, a national survey indicated that about 0.8% of children reported allergy to Peanut (146). Other studies concur, showing that almost 1 in 150 children has a Peanut and/or tree nut allergy (147). In one registry of patients with Peanut allergy, more than 70% had had their first allergic reaction after their first apparent contact with Peanuts. Since reactions require previous exposure for sensitisation, and since IgE antibodies do not cross the placenta, these findings suggest that Peanut protein was encountered in in soe other way in utero, or through breast milk (105,148). In a French study of 54 infants who were less than 11 days old and 71 who were 17 days to 4 months old, 8% had a positive skin-prick test for Peanut (149). Approximately a third of American children with moderate to severe atopic dermatitis and food hypersensitivity are allergic to Peanuts (150).

Peanut allergy is self-reported by 1 in 200 of the British population (151). According to a population-based study of 3- to 4-year-olds in the United Kingdom, the prevalence of sensitisation to Peanuts increased 3-fold from 1.1% to 3.3% from 1994 to 1996. Of 41 sensitised children in a study, 10 reported a convincing clinical reaction to Peanut, and 8 had positive oral challenge results, giving an overall estimate of Peanut allergy of 1.5% (18/1246) (152). Serological evidence of sensitivity to Peanuts from data gathered from 1988 to 1994 indicated that about 6% of Americans had IgE antibodies to Peanut (although the majority would not have an allergic reaction when eating Peanuts) (153).

The prevalence of Peanut allergy in a study of 7768 primary school children in Montreal, Canada, was 1.50%. When multiple imputations were used to incorporate data on those responding to the questionnaire but withdrawing before testing, the estimated prevalence increased to 1.76%. When data regarding the Peanut allergy status of non-responders were also incorporated, the estimated prevalence was 1.34% (154).

In a group of 580 patients in France with reactions to food, 60 presenting with severe, near-fatal reactions, 37% were sensitised to Peanut (155). A second French study of food allergy in 544 children aged 0 to 15 years, who were evaluated with oral food challenges, found that 24% had Peanut allergy and 4% had a tree nut allergy. Clinical symptoms attributed to Peanut allergy included atopic dermatitis (46%), urticaria/angioedema (32%), asthma (15%), generalised anaphylaxis (5%), and gastrointestinal symptoms (3%) (156).

There is good evidence that Peanut allergy is on the increase (145,151,157). When and how does sensitisation occur, and why is it increasing? Several possibilities have been investigated. A factor postulated to have contributed to Peanut allergy in the UK is the cutaneous exposure to ultra-low doses of Peanut antigens in Peanut oil found in diaper rash emollients, which are applied to the skin of infants with eczema or diaper rash (146,158). Differences in the way Peanuts are prepared may contribute to the variations in prevalence. For example, the per capita consumption of Peanuts in China is similar to that of the United States; yet Peanut allergy is very rare in China (113).

First sensitisation has been attributed to the presence of Peanut allergen in breast milk. In a report on 8 infants with immediate hypersensitivity reactions to foods, including Peanut, occurring at the first-known exposure, the most likely route of sensitisation was thought to be breast milk, and reactions were thought to be dose-dependent. Symptoms experienced included irritability, erythematous rash, urticaria, angioedema, vomiting, rhinorrhoea, and cough (159).

Peanut allergy has also been reported to be transferred through liver, kidney (160-161), and bone marrow transplantation (162).

Highly processed oils (acid-extracted, heat-distilled) do not contain Peanut protein (5). However, cold-pressed or extruded Peanut oils contain Peanut protein. This may result in adverse reactions, such as from Peanut oil-based vitamin preparations (8) and infant milk formulae (6). In a study of adverse reactions to crude Peanut oil, 10% of Peanut-allergic subjects reported allergic reactions. Refined Peanut oil did not pose a risk to any of the subjects (5).

Peanut may be a hidden allergen, with very serious consequences. For example, fatal anaphylaxis to ingestion of undeclared Peanut flour was reported (163). The problem is especially severe in that Peanut can result in severe reactions to even minute amounts, and even through skin contact (129,164). Infants have reacted adversely even to breast feeds after maternal consumption of Peanut (165). However, the risk of adverse reactions may be product-specific: casual exposure to Peanut butter is unlikely to elicit significant allergic reactions. The authors, however, warn that the results cannot be generalised to larger exposures or to contact with Peanut in other forms (flour and roasted Peanuts) (166).

But extreme cases should be kept in mind. A 9-month-old male developed localised urticaria when his mother kissed him after she had eaten cereal with milk, and generalised urticaria manifested after his brother ate a Peanut butter sandwich and barely touched his bare leg. His first dose of Egg white as half a teaspoon of meringue caused generalised urticaria and conjunctivitis. Approximately an eighth of a slice of bread caused a similar reaction. Similarly, a 5-year-old developed wheezing when entering a classroom of a teacher who had just eaten Peanuts (167). Peanut allergens may be transferred on playing cards (168). As the fat content of a challenge vehicle has been shown to have a profound effect on the reaction experienced after allergen ingestion, fat content may need to be considered in assessing the risk of certain foods to food-allergic individuals (169).

Reactivity to tree nuts is a serious problem for Peanut-allergic people. Peanut and tree nut allergic reactions coexist in 25-50% of Peanut-allergic patients (117-119). In a study of 62 patients with nut allergy (adults and children), Peanuts were the commonest cause of allergy (47), followed by Brazil nuts (18), Almonds (14), and Hazel nuts (13) (118). Similarly, in a study of 122 children attending a food allergy clinic, 68 experienced acute reactions to Peanut alone, 20 to tree nuts but not Peanut, and 34 to both Peanut and at least 1 tree nut. Of the total of 54 children with reactions to tree nuts, 34 had reactions to 1 kind of tree nut, and 20 had reactions to 2 or more different tree nuts, the most common being Walnut, Almond, and Pecan. First reactions usually occurred at home, and at a median age of 24 months for Peanut and 62 months for tree nuts. The skin was the most common organ affected (89% of reactions, 39% as the only system involved), but the respiratory (52%) and gastrointestinal tract (32%) were also affected (117).

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f201 Pecan nut

Carya illinoensis/Carya illinoinensis

Family:	*Juglandaceae*
Common names:	Pecan nut, Hickory nut
Source material:	Shelled & heated nuts

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Allergen Exposure

Geographical distribution

The large Pecan tree, native to and very common in southern and especially south-eastern North America, is important for its timber and edible nuts. The Pecan nut was a major food source for the American Indians for thousands of years.

The US South yields 250 million pounds of the nuts in an average year, Texas being the largest producer. The tree is planted far beyond this range, however, covering several of the world's warmer temperate zones and subtropical areas.

The Pecan tree bears sweet edible nuts, deep brown in color, that range from 2.5 to 5 cm in length. The nuts have smooth shells and a mild, Walnut-type flavor. Pecan nuts are not produced until trees are 5 or 6 years old. The nuts ripen from mid-September until December in the Northern Hemisphere. They are harvested after they fall to the ground. Pecans can last up to 6 months in their shells if refrigerated.

Environment

Over 100 varieties are commercially available, *e.g.*, Shagbark hickory nuts and Mockernut hickory nuts. They are used whole or crushed. Oil from the nuts is an ingredient in processed foods, is used in the manufacture of cosmetics and soap, and is a drying agent in paints.

Allergens

Only 1 Pecan allergen has been characterised to date:

Car i 1, a 2S Albumin commonly called napin (1-2).

The allergen profile may change as the Pecan matures, is stored or heated. One study demonstrated that IgE antibodies to allergens present in aged or heated Pecan nuts could be detected, but no IgE to any in fresh Pecans. These neoallergenic determinants were located on protein(s) with a molecular weight of approximately 15 kDa (3). Maillard-type reactions may be responsible for the change in allergenicity of the protein (4). Pecan nut allergens in small quantities may result in severe reactions.

Furthermore, analysis of the native and heat-denatured proteins that were previously subjected to *in vitro* simulated gastric fluid digestions indicates that stable antigenic peptides are produced (5).

Potential cross-reactivity

Pecan appears to be highly cross-reactive with Walnut at even the lowest concentrations used, and this correlates with clinical reports of cross-reactivity in the patients in question (6-7). Some degree of cross-reactivity between Peanut and Pecan has been observed (8).

Conformational analysis of the linear IgE-binding epitopes mapped on the molecular surface of Ara h 2 showed no structural homology with the corresponding regions of the Walnut Jug r 1, the Pecan nut Car i 1 or the Brazil nut Ber e 1 allergens. The absence of epitopic community does not support the allergenic cross-reactivity observed between Peanut and Walnut or Brazil nut, which presumably depends on other ubiquitous seed storage protein allergens, namely the vicilins. However, the major IgE-binding epitope identified on the molecular surface of the Walnut Jug r 1 allergen shared a pronounced structural homology with the corresponding region of the Pecan nut Car i 1 allergen. With the exception of Peanut, 2S albumins could therefore account for the IgE-binding cross-reactivity observed among some other dietary nuts, *e.g.* Walnut and Pecan nut (1).

Clinical Experience

IgE-mediated reactions

IgE-mediated allergy to foods containing Pecan nuts is common. Pecan nut allergy frequently has an onset in the first few years of life and generally persists, accounting for severe and potentially fatal allergic reactions (9-12).

The Food Allergy and Anaphylaxis Network (FAAN) Peanut and Tree Nut Allergy Registry in the USA, covering 5149 patients (mainly children), reports Walnut as the first cause of allergic reactions to tree nuts in 34%, followed by Cashew (20%) and Almond (15%). Nine percent of self-reporting tree nut-allergic patients list Pecan as an allergen (13).

Pecan nut allergens may be absent in fresh Pecan nuts, which become allergenic as the Pecan nut protein matures during aging (2-3). Neoallergens may result from the heating process for roasting Pecan nuts, and have been identified as the cause in anaphylaxis in a child who experienced this condition after eating cookies containing these nuts (2).

In a group of 122 children who had experienced acute reactions to nuts, 68 reacted to Peanut alone, 20 only to tree nuts, and 34 to both. Of those reacting to tree nuts, 34 had reactions to 1 type, 12 to 2, and 8 to 3 or more, the most common being Walnut, Almond, and Pecan. Initial reactions usually occurred at home and were thought to result from a first exposure in 72% of cases. Eighty-nine percent of the reactions involved the skin (urticaria, angioedema), 52% the respiratory tract (wheezing, throat tightness, repetitive coughing, dyspnoea), and 32% the gastrointestinal tract (vomiting, diarrhoea). Two organ systems were affected in 31% of initial reactions, and all 3 in 21% of reactions (14).

IgE antibodies would appear to be most useful in confirming the diagnosis of nut hypersensitivity in children or in particularly highly allergic patients for whom skin testing poses a risk of anaphylaxis (5).

Other reactions

Commercial products may contain Peanuts that have been deflavoured and reflavoured and coloured to resemble Walnuts, Pecans, or Almonds. This may result in anaphylaxis in Peanut-sensitive individuals (15).

Protein contact dermatitis from Pecan nut has been reported (16).

A patient is described who experienced an acute vesicular cutaneous reaction after prolonged contact with pecans (17).

f201 Pecan nut

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Pinus edulis

Family:	*Pinaceae*
Common names:	Pine nut, Pignoles, Pinon nut, Pignola, Pinyon nut, Pine kernals
Source material:	Shelled nuts
Synonyms:	*Pinus pinea, P. cembra, P. cembroides*
See also:	Pine t213 and White pine t16

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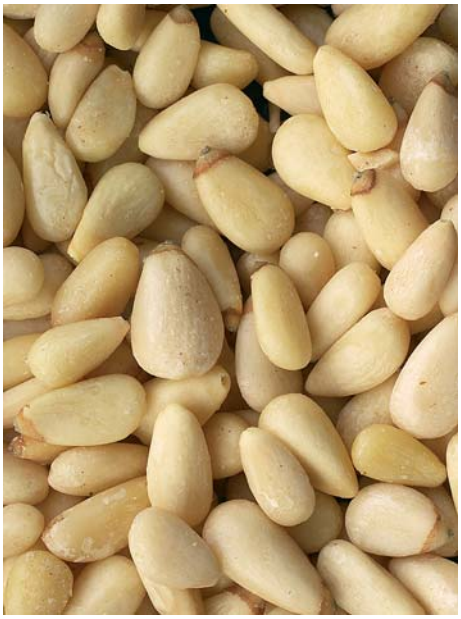

Allergen Exposure

Geographical distribution

Pine nuts, coming from several varieties of Pine trees, are abundant in south-western North America, but also in similar climates elsewhere, most notably the Mediterranean. They were an important food source for Native Americans. The high-fat, high-protein, ivory-coloured nuts are actually inside the Pine cone, which generally must be heated to facilitate their removal. The nuts, though tiny (about 1.5 cm in length), must be taken out of their thin, soft shells as well. This long process is what makes the nuts so expensive.

The Pine nut has in many varieties, including the Italian or Mediterranean and the Chinese.

Environment

Pine nuts are often sold as a health product. They are used raw and intact, ground up, and for oil. They are popular as a snack, in salads, and in sweet and savoury ethnic dishes, especially the classic Italian pesto and as a seasoning in the cuisine of the Mediterranean area of Spain.

Allergens

No allergens from this plant have yet been characterised.

In previous studies, 30 protein bands have been demonstrated in Pine nut, 3 of which (66 to 68 kDa in size) bound IgE in a Pine nut-allergic patient's serum in immunoblot studies (1). A 17 kDa protein has also been detected and found to be sensitive to reducing agents, losing its IgE-binding properties through reduction (2). A 17 kDa protein was isolated by serum from 2 young children who experienced anaphylaxis to this nut (3). Pine nut protein bands of 30 and 44 kDa, which disappear in the inhibition of immunoblotting with Peanut, have been isolated (4). An important allergenic band of 50 kDa, which disappeared after blotting inhibition with an Almond extract, has also been reported (5).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (6). Cross-reactivity between the botanically related seeds of *Pinus pinea* and *P. cembra* has been demonstrated by RAST inhibition (7). It was postulated, based on the cross-reactivity between Pine nut and Pine pollen extracts, that co-sensitisation to these allergens could be the reason for a case of Pine nut allergy described in a single patient with Pine pollen

allergy (8). However, the allergens were not studied in this case, and among individuals who had experienced anaphylactic reactions to Pine nut, none were Pine tree pollen-allergic (3,9).

Studies have also reported the existence of common antigenic proteins between Pine nut and Peanuts (4), and cross-reactivity between Pine nut and Almond (5); however, many individuals with allergy to Pine nut have no IgE antibodies to these nuts and do not experience allergic reactions following ingestion.

Clinical Experience

IgE-mediated reactions

Pine nut may commonly induce symptoms of food allergy in sensitised individuals (5,10-14).

A study reports on 4 paediatric patients with allergy reactions on ingestion of Pine nuts. Ages ranged from 12 months to 6 years. All patients had a history of atopy. Severe systemic reactions occurred in 3 cases. Two of the children had allergic reactions to other nuts. In all cases, both the skin test and the serum IgE antibody test were positive (11).

Reactions may be severe. Anaphylaxis after Pine nut ingestion has been often reported (2,9-10,15-18). Anaphylaxis after eating Pine nut was reported in a 10-year-old boy, who had been previously diagnosed with seasonal rhinoconjunctivitis with sensitisation to grass and Olive pollen (4). A 21-year-old white male developed life-threatening systemic anaphylaxis within seconds of ingesting a small amount of a cookie containing Pine nut. SPT, ELISA, and basophil histamine release studies demonstrated Pine nut-specific IgE antibodies (1). A patient with Bird-Egg Syndrome who experienced an anaphylactic reaction after eating some of her Parrot's food (containing Pine nut) has been reported. Allergen-specific IgE against *Pinus pinea* (Stone pine) was demonstrated by IgE antibody testing (7).

Two young girls who experienced anaphylaxis caused by small amounts of Pine nuts were described. Allergy to Pine nut was confirmed by skin reactivity and IgE antibodies, but negative tests for other nuts and for Pine pollen. The patients had IgE antibodies directed against a Pine nut protein band of approximately 17 kDa that could be considered the main allergen. The 17 kDa protein could be correlated with the severe clinical symptoms. Both girls were monosensitised to Pine nut (3).

A 22-year-old man, without a history of atopy or drug allergy, presented with difficulty in breathing and swallowing, profuse sweating, abdominal pain, and visual disturbances 15 minutes after eating several Pine nuts (2).

Acute anaphylaxis after skin testing for Pine nut was reported in a 20-year-old woman. Her initial complaints were that she had developed generalised urticaria, swelling of the face and dyspnoea after eating a salad containing Pine nuts. Similar symptoms were experienced after the skin test, including a strong local skin reaction (19).

Anaphylaxis to Pine nuts was described in a 53-year-old man, who experienced angioedema, acute dyspnoea and circulatory collapse for the first time after a meal of spaghetti and pesto sauce (olive oil, herbs, Pine nuts and sardines). Skin reactivity was demonstrated for Pine nut but not for the other ingredients. Ten minutes after an oral challenge of a teaspoonful of Pine nuts, he developed marked conjunctival inflammation and periorbital itching and reddening. The IgE antibody level for Pine nut was Class 4 (17).

Anaphylaxis to Walnuts and Pine nuts induced by ACE inhibitor has been documented (20).

A number of collections of case reports have further extended the understanding of the implications of Pine nut allergy.

In a study of Pine nut allergy, three case reports are given:

A 43-year-old female suddenly experienced anaphylaxis while eating in a Polynesian-style restaurant. SPT for common Oriental food ingredients were all

negative. The chef disclosed that crushed Pine nuts were used in the salad. SPT with a Pine nut extract was positive within 3 minutes, and a 18 x 24 mm wheal, which featured pseudopodia and intense pruritus, had formed at 10 minutes. Contact with other sources of Pine, such as natural Pine resins, bark and needles, was not associated with any immediate or delayed respiratory, skin or other reactions in this patient (10).

The second case was of recurrent urticaria in a 28-year-old woman. She noted a spreading urticaria about an hour after eating a dish containing Pine nut. She was initially unable to identify the cause of this skin reaction, but about 5 months later, she had a recurrent and more severe urticarial episode, which she attributed to Pine nut. She was reluctant to be tested, but when a whole Pine nut was rubbed on her forearm, she developed erythema and a wheal, followed by a slightly scaly, rough, eczematoid eruption that lasted 3 or 4 days. Notable, she had consumed "2 or 3 glasses" of a resin-flavoured wine (Greek retsina, a white or rosé wine flavoured with Pine resin) without any reaction suggestive of allergy. External contact with Pine and other evergreen products did not appear associated with any clinical hypersensitivity in her case either (10).

The third case was of a 17-year-old male student with a history of multiple food sensitivity, including dermal, respiratory and gastrointestinal reactions to a variety of "nuts". Almond had caused "stomach upsets"; Peanut (and other legumes) were blamed for asthma-like symptoms, and Pistachio had reportedly caused stomatitis and epigastric pain. Skin reactivity for Pine nut was present, but an oral challenge "did not appear then - or subsequently - to be of any practical benefit to this multiply atopic individual". The authors nevertheless advised him to avoid Pine nut (10).

Severe anaphylaxis to Pine nut was described in 3 patients. A 28-year-old chef presented with generalised urticaria, swelling of the face, acute dyspnoea, and pulmonary collapse a few minutes after eating a salad dressing containing Pine nut. SPT for some tree nuts and Peanut, among other substances, were negative, but positive for Pine nut. Pine nut-specific IgE was 11 kU_A/l. A second patient, a 35-year-old man who had presented with 2 episodes of anaphylaxis following ingestion of Pine nuts, reported that within minutes after ingestion, he had developed generalised urticaria, facial swelling, acute dyspnoea, and pulmonary collapse. He also reported generalised urticaria after eating Brazil nut. SPT was negative to a number of allergens, including Hazel nut, Almond and Peanut, and positive to Brazil nut, Chestnut, Walnut and Pine nut, among other allergens. Pine nut-specific IgE was 6.25 kU_A/l and raised for Brazil nut and Chestnut. The third patient, a 19-year-old man, developed facial angioedema, acute rhinoconjunctivitis, and asthma rapidly after eating pesto sauce. He had previously experienced generalised urticaria after handling Pine nut. SPT was negative for Peanut and some tree nuts, except for Pine nut. The IgEantibody level was 79.9 kU_A/l. None of the patients was Pine pollen-allergic (9).

Two further cases are also illustrative. A 23-month-old girl had during 3 months experienced moderate respiratory difficulty following ingestion of a small amount of Pine nut; she then experienced 2 episodes of angioedema of the eyelids, lips, face and feet. She had a third episode immediately after sucking Pine nuts: angioedema, wheezing and acute dyspnoea requiring emergency treatment. The patient tolerated normal food in her diet, including Almond, Walnut, Hazel nut and other nuts (3). A second patient, a 15-year-old girl, had at the age of 4 suffered severe urticaria, angioedema of the lips and eyelids, laryngeal oedema, hoarseness and dizziness after ingestion of a single Pine nut. At the age of 14, she had an episode of anaphylaxis, with vomiting, itching of the mouth, oedema of the tongue and larynx, general urticaria, severe respiratory difficulty, cyanosis and thoracic pain after eating a sausage that the authors suggest may have contained Pine nut. She tolerated Peanut, tree nuts and Sunflower seed. In both patients, SPT was negative to tree nuts and Pine tree pollen, but positive for Pine nut. Allergen-specific IgE for tree nut and Peanut were negative, and respectively 7 and 1.7 kU_A/l, for Pine nut. Both girls were monosensitised (3).

f253 Pine nut

Allergy to Pine nut has been described in a patient who showed no clinical symptoms to Pine pollen despite the presence in her serum of Pine tree pollen-specific IgE. SPT with fresh Pine nut and IgE antibody evaluation with Pine nut and Pine pollen extracts showed high levels of IgE against both. Immunoblotting experiments showed the presence in serum of IgE antibodies against several components of Pine nuts and pollen. Immunoblotting inhibition experiments demonstrated the presence of some cross-reacting components. This data confirmed the existence of food allergy induced by Pine nuts, but there were no symptoms of Pine pollen allergy. The authors suggest that the development of pollinosis may require a longer period of exposure to allergens but that, because of the cross-reactivity between Pine nut and Pine pollen extracts, co-sensitisation to these allergens could be possible (8). Similarly, a study reported on 3 individuals with Pine nut allergy and Pine pollen sensitisation (21).

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Pistacia vera

Family: *Anacardiaceae*

Common names: Pistachio, Pistachio nut

Source material: Shelled nuts

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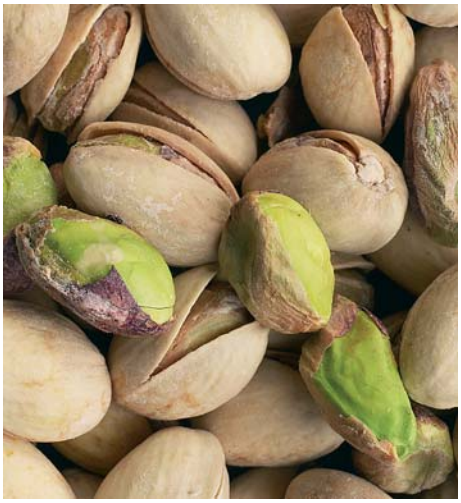

Allergen Exposure

Geographical distribution

Pistachio is a green, edible seed obtained from the Pistachio tree, which belongs to the *Anacardiaceae* (Sumac) family, along with Mango and Cashew nut. The Pistachio tree grows up to 10 m high and has deciduous pinnate leaves up to 20 cm long. It is native to the mountainous regions of central and south-western Asia. Pistachio is now cultivated in other parts of the world, particularly in California and Australia.

The plants are dioecious, with separate male and female trees. The flowers have no petals and are borne in panicles. Pistachio harvests are heavier in alternate years. The fruit is a drupe (in culinary but not botanical terms a nut), containing an elongated seed with a hard, whitish shell around 2 cm long and a striking light green kernel. It has a very characteristic flavour. When the fruit ripens, the shell splits partway open with an audible pop, but the nut remains enclosed and is usually marketed in this state as a snack. The shell of the Pistachio is naturally a beige colour, but it is sometimes dyed red for commercial sale.

Pistachio is often confused with some of the other 9 species in the genus *Pistacia*, such as *P. terebithus* and *P. lentiscus*. These species have a different distribution, in the Mediterranean and south-west Asia, and have much smaller nuts, lacking the hard shell of *P. vera*.

Environment

Pistachio nuts are widely used in the catering industry in ice creams, cakes and other confectionary, mortadella (a sausage) and oriental dishes. They are also eaten roasted as a popular snack.

Oil is processed from the seed and may pose a threat to patients with allergy, depending on the method of manufacture and processing (1).

Pistachio nuts are reported to be highly flammable when stored in large quantities, and are prone to self-heating and spontaneous combustion.

Allergens

A number of allergens have been isolated, and some characterised (2).

In 3 adults with anaphylaxis to Pistachio, allergenic proteins of 34, 41, 52 and 60 kDa were found (3). In a similar study of 3 patients who had experienced anaphylaxis to Cashew nuts and were sensitised to the close family member Pistachio, both nuts were shown to have several IgE binding protein bands, the strongest of these bands having similar molecular weights of 15, 30 and 60 kDa (4). In an investigation of 2 children who had experienced anaphylaxis to Pistachio, IgE binding was found to be strongest in 3 bands between 30 and 41 kDa, the strongest at the 34 kDa band (5).

f203 Pistachio

The following allergens have been characterised:

Pis v 1, a 2S albumin (2,4).

Pis v 2, an 11S globulin (6).

Pis v 3, a vicilin-like protein (6).

Pis v 4, a magnesium superoxide dismutase (6).

A lipid transfer protein (LTP) may be present, as suggested by a study of lipid transfer proteins in *Rosaceae* members which found that the *Rosaceae* LTP reacted to a broad range of foods, including Pistachio (7).

Preliminary evidence for the presence of a 2S albumin has been reported (4).

Potential cross-reactivity

The close relationships among the *Anacardiaceae* suggest cross-reactivity, and this is supported by studies demonstrating cross-reactivity between Cashew and Pistachio (8). In a study of 42 children with Cashew allergy, 7 had an associated food allergy to Pistachio (9).

By means of serum from 2 children with Pistachio nut allergy, both were shown to be reacting to several Pistachio and Cashew allergens with common antigenic determinants. Cross-reactivity was also found between Pistachio nut and Mango seed, but not Mango pulp (5).

In a study of 3 individuals who experienced anaphylaxis to Cashew nut, all demonstrated IgE antibodies to Cashew and Pistachio. Evaluation of the allergen found that the strongest IgE-binding bands had similar molecular weights and that a 15 kDa protein band may have been a 2S albumin panallergen (4). Whether further cross-reactivity occurs as a result of other foods containing the 2S albumin has not been evaluated, but cross-reactivity has been demonstrated between Pistachio, Peanut, Walnut and Sunflower seed (3), all known to contain the albumin; and similarly, cross-reactivity has been reported to occur among allergens in Sesame seed and allergens in other foods, including Hazel nut, Rye, Kiwi, Poppy seed, Black walnut, Cashew, Macadamia, Pistachio, and Peanuts (10).

Cross-reactivity among Pistachio, Mango (14) and Artemisia (11) has been suggested. Sensitisation to Pistachio is common in *Parietaria* allergy (12). Cross-reactivity may also occur between Pellitory and Pistachio (13).

Cross-reactivity with other lipid transfer protein-containing foods is possible (6).

As Pistachio contains an 11S globulin (Pis v 2) and a vicilin-like protein (Pis v 3), cross-reactivity with other foods containing these allergens is possible, but it has not been elucidated as yet.

Cashew nut, and possibly Pistachio nut, allergy may be associated with pectin allergy, and the possibility of pectin allergy should be considered in Cashew- or Pistachio-allergic patients who have unexplained allergic reactions. A study describes a 3 1/2-year-old boy who developed anaphylaxis after eating Cashew nut and later after eating a pectin-containing fruit "smoothie". The child had skin reactivity to pectin and a high IgE antibody level to Cashew nut and Pistachio nut, as well as a low levels to Grapefruit, to which he had previously also reacted. The pectin in the smoothie was confirmed to be of citrus origin (14).

Clinical Experience

IgE-mediated reactions

Pistachio may uncommonly cause symptoms of food allergy in sensitised individuals. Adverse reactions are similar to those seen with other tree nuts and include symptoms of oral allergy and food allergy, cutaneous manifestations, angioedema and severe anaphylaxis (3,5,15-16). Most of these reports have concerned small children. The IgE-mediated mechanisms have been confirmed with SPT and IgE antibody testing (5). As more exotic foods are introduced into more countries, more reactions are likely to be seen (17).

Two children were described as having allergy to Pistachio nut. Skin reactivity for Pistachio and Cashew were detected in both, and for Mango seed in one. IgE antibodies for Pistachio and Cashew nut were found in both (5).

Two uncommon cases of oral allergy syndrome after eating Pistachio nuts were reported, involving a 54-year-old man and a 3-year-old girl. Both were shown to have skin reactivity for *Parietaria* and Pistachio nut. A double-blind, placebo-controlled food challenge was performed on the adult patient and was negative, but a positive intraoral reaction was noted when the oral mucosa was slightly scratched. It was suggested that breaking the shells with his teeth had slightly injured the oral mucosa, which had enhanced the local response and resulted in symptoms (14).

Anaphylaxis to Pistachio has been described in 3 individuals who were allergic to both Mango and Pistachio nut. The individual history of each is informative. One, a 3-year-old boy, developed facial oedema and inspiratory stridor within minutes after eating Pistachio ice-cream. After eating a single Pistachio nut on a subsequent occasion, he developed generalised itching, hives and facial angioedema. A 28-year-old woman developed generalised urticarial eruptions on 2 separate occasions after ingesting Paprika, Curry and Celery. Three months later, she complained of a burning sensation in her mouth, swelling of the lips, face and tongue, and nausea and abdominal cramps immediately after eating a Mango. A 28-year-old man experienced episodes of generalised itching and hives, profuse sweating, abdominal pain, nausea and vomiting immediately after eating Peanut, Peach, Paprika, Hazel nut or Mango, on different occasions. Two of these patients were found to have skin reactivity to Pistachio. All were found to have skin reactivity to fresh Mango but not to Mango extracts of peel or pulp (15).

Anaphylaxis has also been reported in 3 other adults (3).

Food-dependent exercise-induced anaphylaxis to Pistachio has been described in a 16-year-old boy; it occurred 30 minutes after he began to play football after having ingested Pistachio nuts. SPT evaluation using roasted Pistachios was negative. No allergen-specific IgE antibodies were detected to Pistachio, Cashew Nuts or Mango. An open oral challenge test with Pistachio in resting conditions was negative. A specific food exercise challenge using a treadmill ergonometric stress test was positive 60 minutes after the patient had ingested 50 g of Pistachio nuts, with the onset of mild diffuse erythema and small wheals on his face and thorax (18).

In a study of 42 French children with Cashew allergy, 7 were found to have an associated food allergy to Pistachio. The authors stated that the increase in Cashew allergy was of concern because it affects young children who may have a reaction without ever having been exposed to Cashews. One could surmise that this may be valid for the close family member Pistachio as well (8). Indeed, it has been recommended that Pistachio be included in the list of foods to be tested in the investigation of anaphylactic reactions of unknown origin in small children (5).

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Papaver somniferum

Family: *Papaveraceae*

Common names: Poppy, Opium poppy, Blue bread seed poppy, White poppy

Source material: White & blue seeds

Important other varieties are:

Papaver rhoeus L., known as Corn or Field poppy, and native to Europe and Asia; the alkaloids rhoeadine, morphine, and papaverine have been reported in this species.

Papaver orientale L., formerly *Papaver bracteatum Lindl.*, a morphine-free alkaloid source, used medicinally.

Mexican or Prickly poppy, *Argemone mexicana L.*, reported to have toxicological properties

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Allergen Exposure

Geographical distribution

Poppy is an annual herb native to south-eastern Europe and western Asia. There are wild and cultivated varieties. The species is cultivated extensively in many countries, especially in Asia and Central and South America.

The plant can reach a height of 1.2 m. It can have white, pink, red, or purple flowers and is an important ornamental. Seeds range in colour from white to blue-black. The seeds are rather small, but there are large numbers of them contained in capsules 3 cm or more in diameter, and so they are easy to harvest and utilise. They are often eaten as flavouring but can also be processed as drugs, including the illicit drugs opium and heroin.

Environment

Poppy seeds are employed raw or cooked. They are used as flavouring in cakes, bread, fruit salads, etc. The crushed and sweetened seeds are a filling in certain crêpes, strudels, and other pastries. The seeds are perfectly safe to eat, containing very little if any of the narcotic principles; however, they have been reported to cause false positives on drug tests. The seeds are highly nutritious. A high-quality edible drying oil, also not narcotic, is obtained from the seed and makes a good substitute for olive oil. The young leaves, raw or cooked, are edible and probably do not contain narcotic principles, but caution is advised.

The latex from the unripe green seed contains a wide range of alkaloids (including morphine, opium, codeine, noscapine, papaverine, thebaine and narcotine) and yields valuable medicines, especially useful in bringing relief from pain. But this substance (and especially the opium and morphine it contains) can cause addiction and so should be treated with extreme caution and used only under the supervision of a qualified practitioner.

Unexpected exposure

Seeds of the plant are not always apparent or noticed when used in bakery products. Poppy seed is sometimes used as a colouring in cough syrups and other products.

f224 Poppy seed

Poppy seed is sometimes used for its oil, which can also be a "hidden allergen". The Poppy seeds and the fixed oil that can be expressed from them are not narcotic, because the seeds develop after the capsule has lost its opium-yielding potential. However, the narcotic principles are still present and may be detected in urine sampling.

Poppy oil is used for lighting, and in the manufacture of paints, varnishes, and soaps. Poppy latex features in a number of medicinal products.

Allergens

The following allergens from this plant have been isolated:

Pap s 17kD, a Group 1 *Fagales*-related protein, a Bet v 1 homologue (1).

Pap s 34kD (1).

Pap s Profilin (1).

In a study of sera of 11 Poppy seed-allergic patients, specific IgE from the sera of 10 bound to a 45 kDa, 4 to a 34 kDa, 5 to a 17 kDa, 5 to a 14 kDa, and 3 to a 5 kDa protein. Individual IgE binding to proteins of 20, 25, 30 and 40 kDa was also seen. The 40 and 45 kDa allergens were glycoproteins and contained IgE binding carbohydrate moieties. Cross-reacting homologues of pollen allergens, including Bet v 1 and profilin, were detected in Poppy seed extract (1).

In individuals with occupational asthma from working with shells of *P. somniferum*, a major protein band with an estimated size of 52 kDa was detected (2).

Potential cross-reactivity

An extensive cross-reactivity among the various individual species of the genus and family, including the Californian poppy (*Eschscholzia californica*), the Mexican poppy (*Argemone mexicana*) and celandine (*Chelidonium majus*), could be expected (3).

Poppy seed contains homologues of Bet v 1 and profilin, which indicates the possibility of cross-reactivity with other plants containing these panallergens. Nine of 11 patients in a study of allergenicity to Poppy seed showed concomitant IgE binding to allergens of Birch, Mugwort or grass pollen in laboratory tests. They reported characteristic seasonal symptoms (1).

Allergy to Kiwi, Poppy seeds, and/or Sesame seeds has been reported to occur often in patients with a simultaneous sensitisation to nuts and flour. In a study investigating this association, the degree of cross-reactivity among Kiwi, Sesame seeds, Poppy seeds, Hazel nuts, and Rye grain was found to be very high in the patients studied. The existence of both cross-reacting and unique allergens was observed; however, the cross-reacting and unique allergens could have been different for different patients (4).

A study describes 3 patients with severe immediate-type allergic reactions to Poppy seed, all of whom had serum showing IgE antibody binding specific for Sesame seed. The authors considered that this might be due to a cross-reactivity to similar allergens (5).

In a report of a 17-year-old female with an apparent allergic reaction from ingestion of a Poppy seed cake, a novel allergen causing cross-sensitisation to Buckwheat was described (6).

Clinical Experience

IgE-mediated reactions

Poppy seed commonly induces symptoms of food allergy in sensitised individuals, which may be confirmed by SPT and IgE antibody determination. It has been suggested that the prevalence of Poppy seed allergy is increasing as a result of the increased number of vegetarian and ethnic dishes.

Immediate-type allergic reactions range from mild local symptoms to severe anaphylactic reactions, and may involve the gastrointestinal, respiratory or skin systems (1,7-10). A patient who experienced an immediate-type hypersensitivity reaction against Poppy seed described symptoms of swelling of the oral mucosa, vomiting, respiratory distress, and urticaria. Poppy seed-specific IgE was demonstrated (5).

Other studies have described similar severe immediate-type reactions to Poppy seed; these studies include a report of 3 patients in whom SPT and IgE antibody test were positive (5). Immediate-type allergy caused by Poppy seed in a 52-year-old man was described. Symptoms included epigastric pain, angioedoema, and respiratory distress a few minutes after eating Poppy seed cake. SPT and IgE antibody test were positive (7). A 17-year-old female had an apparent food-allergic reaction after ingestion of a Poppy seed cake. Laboratory investigation led to the identification of a novel cross-sensitisation with Buckwheat (6).

Anaphylaxis and food-dependant exercise-induced anaphylaxis have been reported (11-12). Food-dependant exercise-induced anaphylaxis was described in a 46-year-old man who had experienced 4 episodes of generalised urticaria, all occurring within 1 hour after ingestion of a Poppy seed cake. These episodes occurred only in combination with exercise, although he had been eating this cake every Friday for about a year. SPT for Poppy seed was positive and allergen-specific IgE was 13.4 kU_A/l. Oral challenges without exercise were negative. On follow up, the patient reported that he had continued to eat Poppy seed cake every Friday, but that only in combination with gardening had generalised urticaria occurred (13).

A study described immune and non-immune hypersensitivity reactions to Poppy seed in a 21-year-old woman and a 32-year-old man, in both of whom life-threatening symptoms and signs of anaphylaxis developed after consumption of Poppy seeds in various situations, *e.g.*, after consumption of a roll with Poppy seeds on it, and of a cake prepared on a moulding board on which Poppy seed paste had previously been squeezed. The female patient was reported to have a history of atopy, and in her case skin reactivity was detected to a range of pollen allergens and to Hazel nuts, whereas SPT for various allergens was negative for the male. In the female, the IgE antibody levels were raised for Celery and nut mixture but negative for Poppy seed, whereas in the male the IgE antibody levels for Poppy and nut mixture were both raised (Class 2). In the male patient, among SPT with topical anesthetics and narcotic analgesics derived from Poppy, tests were positive for xylocaine and codeine. The authors concluded that hypersensitivity to Poppy seed may occur through IgE-dependent or non-immune mechanisms, and that a history of atopy is not completely determinant (13).

Inhalation of Poppy seed resulting in erythema, angioedema, conjunctivitis, and dyspnoea in a 16-year-old boy was described. Skin reactivity was present for Poppy seed, Hazel nut, and Chickpea. IgE levels for Poppy seed, Hazel nut, and Peanut were 3.36 kU_A/l, 1.5 kU_A/l, and 6.17 kU_A/l, respectively. This is the first report on inhalant allergy to Poppy seed (14).

Allergic contact dermatitis and contact urticaria have been reported to closely related family members, *Papaver rhoeas* and *Papaver nudicaule* (Icelandic poppy) (15-16).

Other reactions

IgE reactions have also been reported to Poppy shells, which contain the seeds. Six of 28 workers in a pharmaceutical factory producing morphine and extracting other alkaloids from shells of *Papaver somniferum* were found to have clinical symptoms of sensitisation to Poppy. Skin reactivity was demonstrated. A bronchial provocation test was found to be positive for 4 workers, and in all of these cases IgE antibodies were demonstrated to an aqueous extract of *P. somniferum*. Histamine release tests using the same antigen were also positive in the 4 samples from sensitised patients. A major protein of around 52 kDa was isolated. These findings suggest that *P. somniferum* allergy is mediated by an IgE mechanism and not by a pharmacological or toxic effect of the alkaloids or polyphenols (2).

This plant contains a number of very toxic compounds, many of which are extracted and used as pain killers, etc. They are also used to make various narcotic drugs, which do not all fit the stereotypes of highly refined "street drugs". Danish Poppy capsules contain 3-5 mg morphine per capsule, and the content of morphine in

opium exuded from the capsules may amount to 24%. This has resulted in misuse, as both fresh and dried Poppy capsules can yield "opium tea". During the period 1982-1985, 7 casualties occurred among drug addicts in Denmark that were solely or partly caused by these Opium capsules (17). A patient presenting with dependence on Opium poppy tea has also been reported. But Poppy tea drinking, although previously described in certain parts of the UK, rarely presents as a dependence syndrome (18).

Because Poppy seed may be an ingredient in ordinary confections, caution is warranted in environments with drug testing. In a study in which 9 volunteers ingested cake containing Poppy seed, several urine specimens contained morphine with concentrations higher than 1 microg/ml, and the peak values were approximately 10.0 µg/ml. Because the International Olympic Committee has set a cut-off for morphine at 1 µg/ml, athletes could fall foul of testing after consumption of products containing Poppy seeds (19).

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f226 Pumpkin seed

Cucurbita pepo

Family:	*Cucurbitaceae*
Common names:	Pumpkin, Field pumpkin, Naked-seeded pumpkin, Pimpkin
Source material:	Peeled seeds
Synonyms:	*C. moschata*, *C. maxima*, *C. mixta*, *Cucumis pepo*
See also:	Pumpkin f225

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Allergen Exposure

Geographical distribution

The Pumpkin is thought to have originated in Central America, possibly Mexico, but it is now grown widely in both temperate and tropical zones. It is an annual climber, typically with a large, round, ribbed, edible orange fruit. But Pumpkin comes in several other forms, such as the finer-textured, straw-colored Cheese pumpkin, the Gem squash and the Winter squash. All of these have a hard, smooth rind, sometimes lightly ribbed, covering edible flesh and the central seed cavity. Varieties within and between species can cross-pollinate to produce hybrids: hence the great number of shapes and sizes. Pumpkins, however, can be differentiated from other squashes by their fruit stalk: it is angular and polygonal in Pumpkins but thick, soft and round in other squashes.

Pumpkin seeds are consumed as a snack in many cultures throughout the world and are especially popular in Central American countries, where strains have been selected primarily for edible seed use. World production of the seed for food, on the other hand, is meagre.

Environment

The seeds, with their hulls intact, can be roasted or deep-fried and eaten as a salted snack, like nuts. Pumpkin seeds are a source of vegetable oil, but it is difficult to obtain because the seed is small and the fibrous hull must be removed. Flour may also be produced, and mixed with other cereals for making bread, etc. Fish bait is made from the seeds as well. The seeds can be sprouted and used in salads, etc. Pumpkin seeds are rich in protein.

The seeds are often used for medicinal purposes. (They are especially popular for tapeworm removal in pregnant women and small children, for whom harsher remedies are unsuitable.)

Unexpected exposure

The oil of the seed is sometimes used for lighting, but if pure, should contain no allergens.

Allergens

No allergens from this substance have yet been characterised.

f226 Pumpkin seed

In 3 Pumpkin seed-allergic individuals, immunoblot technique was used to isolate allergens of 13, 14, 36, 48, 77, and 87 kDa. The 14 kDa allergen appears to be a profilin (1).

Whether similar allergens are present in the seed and pulp has not yet been determined. Pumpkin pulp contains an ascorbate oxidase and a profilin (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected, as well as to a certain degree among members of the family *Cucurbitaceae* (3). Clinical cross-reactivity has been demonstrated among Pumpkin, Pumpkin seed, Muskmelon, Watermelon, Cucumber and Zucchini (4).

A cDNA clone encoding a Soybean allergen, Gly m Bd 28K, has been isolated, which exhibits high homology with the proteins in Pumpkin seeds and with a Carrot globulin-like protein. The clinical significance of this has not yet been determined (5).

Clinical Experience

IgE-mediated reactions

Pumpkin can induce symptoms of food allergy in sensitised individuals (4). Dermatitis, asthma, rhinoconjuctivitis, itching of the mouth, angioedema of the face and lips, generalised itching and mild dyspnoea after eating Pumpkin soup or vermicelli made with Pumpkin have been reported in a patient (4). Similar symptoms have been reported in 3 individuals after ingestion of roasted Pumpkin seed. All the patients fished for sport and used pressed Pumpkin seed flour as bait. IgE antibodies were detected to proteins from Pumpkin seed extract. Inhalation of Pumpkin seed flour during fishing was suggested as the route of sensitisation, leading to food allergy to Pumpkin seed (1).

Other reactions

Pumpkin seeds may be aspirated into the trachea in young children (6).

The sprouting seed produces a toxic substance in its embryo.

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Chenopodium quinoa

Family:	*Amaranthaceae* (*Chenopodiaceae*)
Common name:	Quinoa
Source material:	Dried seeds
See also:	Goosefoot / Lamb's quarters w10

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Allergen Exposure

Geographical distribution

Quinoa (pronounced "keen-wa") has been cultivated in the Andean highlands since 3,000 BC. Its small, very nutritious seeds resemble millet and are very versatile in cooking.

Chenopodium plants have characteristic leaves shaped like a goose foot. (The genus also includes a common weed, Goosefoot or Lamb's quarters.) Quinoa is a small seed that in size, shape, and colour looks like a cross between Sesame seed and Millet. It is usually a pale yellow colour, but species vary from almost white through pink, orange, red, purple and black. Quinoa is not a true cereal grain but is technically a fruit of the *Chenopodioideae* subfamily.

Environment

Quinoa is a versatile ingredient, and the dishes it features in range from staple foods to spicy delicacies. Quinoa flour, ground from whole seeds, has a delicate, nutty flavour. A gluten-free product, it is suitable for anyone afflicted by Wheat allergies. Quinoa seeds are naturally coated with a bitter-tasting saponin that protects them from birds and insects.

Allergens

No allergens from this plant have yet been characterised.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but has not been described to date (1). Closely related family members include the weed Goosefoot or Lamb's quarters, which may be of relevance for pollen exposure.

Clinical Experience

IgE-mediated reactions

Quinoa may rarely induce symptoms of food allergy in sensitised individuals.

Other reactions

Saponin, a component of the pericarp of Quinoa seed, is a known toxic glycoside. Saponin can be found in the pericarp of several other species such as Alfalfa, Hops, and Soybean and is easily identified by production of a soapy lather when placed in water, and by solubility in pure alcohol. It also gives unwashed Quinoa a bitter flavour and has antinutritional properties.

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f316 Rape seed

Brassica napus

Family: *Brassicaceae*

Common names: Rape seed, Rapeseed, Canola, Oilseed Rape

Source material: Whole seeds

See also: Rape w203

Brassica napus is a quite variable species, with 3 important subspecies:

B. napus napobrassica (rutabagas or swedes)

B. napus pabularia (Siberian kale, Hanover salad, etc.)

B. napus oleifera (Rape seed)

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Allergen Exposure

Geographical distribution

Rape is an annual plant similar to the turnip and rutabaga. It is thought that *Brassica napus* originated from a hybridisation between the turnip (*B. rapa*) and kale (*B. oleracea acephala*). Rape originated in northern Europe and was cultivated near the Mediterranean Sea, but is now grown throughout the world. Canola, a selectively bred variant of Rape, was developed in the late 1970s in Canada as a more nutritious source of vegetable oil than Rape seed.

The Rape plant is an annual or biennial growing up to 1.2 m, with yellow flowers that in their season make Rape fields a striking sight. At the same time, the released volatile organic compounds (there are 22 altogether (1)) create a distinct smell. The slick, turnip-like flat leaves are 10 to 30 cm long. Unlike turnip, Rape has no swollen root, only a thin taproot. Sickle-shaped pods containing tiny round seeds are produced.

Environment

This plant has become a very common crop in the UK and elsewhere. Rape is generally grown in large fields for green livestock fodder, birdseed or Rape seed oil. Canola is a new type of Rape grown commercially for the seed, which is lower in saturated fats and fatty acids than the original cultivar. Canola oil is also almost free of erucic acid, a toxic compound plentiful in older varieties.

Unexpected exposure

Canola oil has become a common ingredient in both homemade and commercial foods.

Allergens

Rape seed contains 2 main storage proteins, a high-molecular-mass legumin-like 12 S globulin and a low-molecular-mass 2 S protein (also known as napin or nIII) (2-4,6, 9).

The 2 S protein has been characterised as the following:

Bra n 1, a 2S albumin (napin); the protein consists of 2 different chains of 9.5 and 4.5 kDa (5-12).

In a study to identify possible major allergens in Rape seed and Turnip rape using sera from 72 atopic children with positive SPT to these proteins, major reactivity was

demonstrated to a group of homologous, approximately 9.5 to 14.5 kDa proteins that were identified as 2S albumins (napins). Approximately 80% of the patients had IgE antibodies to purified napins from both plants. In SPT using purified napins, positive reactions were demonstrated in all 6 children tested (12).

Rape seed is able to generate chitinase when wounded, as demonstrated by a study in which complementary and genomic DNA strands coding for a *Brassica napus* chitinase have been cloned and sequenced (13-14). The allergenic potential of this protein is not known to date.

Low-molecular-mass trypsin isoinhibitors have been isolated (but their antigenicity is unknown) (15).

A 2S albumin recombinant protein from the seeds of *Brassica napus* was shown to have a high thermal stability, and these results suggest that rproBnIb, like other 2S albumins, may be able to reach the gut immune system intact (11).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the family could be expected to occur clinically with Rape seed (16). A study of children sensitised to Rape seed reported that the high correlation in the skin reactivity between Rape seed and Turnip rape suggested cross-reactivity, and this is supported by the fact that they both contain homologous 2S albumins (17).

The 2S albumin storage protein in Rape seed exhibits extensive sequence similarity with 2S albumins from other seeds. Cross-reactivity between Mustard and Rape seed flours as a result of this protein has been reported (6). Similarly, the Mustard allergen Sin a 1 was found to be related to other low-molecular-mass albumins, such as those isolated from Rape seed, Castor bean and Brazil nut. Structural similarity was also reported between the glutamine-rich large chain of Sin a I and a proline-rich zein, a gliadin, and trypsin and alpha-amylase inhibitors isolated from the seeds of several monocotyledons (18).

Clinical Experience

IgE-mediated reactions

Rape seed protein may induce symptoms of allergy in sensitised individuals, predominantly in occupational settings such as animal feed factories, grain mills and farms. Individuals may be sensitised to either Rape seed as a food or Rape seed pollen as an inhalant. For allergy to the pollen, see Rape w203.

A 48-year-old man who had been working in a feed processing plant suffered episodes of wheezing with shortness of breath after exposure to Rape seed flour. After 5 years of exposure, he noted sneezing and rhinorrhoea whenever the flour was being discharged from the mill and he was in the vicinity. Symptoms subsided 2 hours after the exposure ended. He also developed oedema and pruritis of the lips, oral mucosa and pharynx, and facial urticaria immediately after ingestion of a small amount of Mustard sauce. The reactions were attributed to cross-reactivity with the 2S albumin allergen from Rape seed flour and Sin a 1 from Mustard (6).

A 48-year-old man, employed in a grain and animal feed store for 9 years, reported rhinorrhea, sneezing, nasal obstruction, ocular burning, coughing and wheezing, which had all occurred over the previous 12 months and were induced by Rape flour (19).

A 43-year-old male working in the grain industry experienced cough and chest tightness during working hours. SPT was positive to Rape extract. A broncho-provocation test was positive. The study results confirmed that the inhalation of Rape dust, not pollen, was the cause of his IgE-mediated occupational asthma (20). Similarly, a study demonstrated that inhalation of Rape flour caused bronchoconstriction, induced an eosinophilic inflammatory bronchial response, and increased bronchial hyperresponsiveness in sensitised asthmatic farmers. Contact with the allergen took place through its presence as flour in animal fodder (21).

f316 Rape seed

In a Finnish study, skin prick testing for suspected food allergy in young children with atopic dermatitis frequently found positive reactions with Turnip rape and Rape seed. A subsequent study of 1,887 Finnish children, who were screened with SPT for sensitisation to Turnip rape and Rape, found that 206 (10.9%) had reactivity for Turnip rape and/or Rape seed (9.3% for Turnip rape and 9.4% for Rape seed). Twenty-five (89%) of 28 children enrolled in the challenge study showed a positive challenge reaction to Turnip rape. Seventeen reacted with labial whealing after labial challenge, and 8 had facial urticaria, flare-up of atopic dermatitis or abdominal symptoms after oral challenge. One child developed rhinitis. Four children had immediate symptoms within 3 hours, and 4 experienced delayed reactions. Allergen-specific IgE determination for Turnip was positive in 17 of those positive to labial challenge. Three challenge-positive children showed a flare up of atopic dermatitis when the oral challenge had lasted for 2-5 days. The high correlation in skin reactivity between Rape seed and Turnip rape suggested cross-reactivity, and this is supported by the fact that both substances contain homologous 2S albumins (17).

In a subsequent study, 64 of these children, with atopic dermatitis and the presence of skin reactivity IgE to Turnip rape and/or Oilseed rape, were assessed for any common sensitisation pattern to certain foods or pollens, and were shown to have significantly more prevalent skin- and serum-specific sensitisation to various foods (Cow's milk, Egg, Wheat, Mustard) and pollens (Birch, Timothy, Mugwort) than a control group (22).

Other reactions

Pure Rape seed oil is reported not to cause allergic reactions (23). However, occupational allergic contact dermatitis from PEG-4 Rape seed amide in massage oil has been reported (24).

In the 1980s, Spanish toxic oil syndrome occurred as a result of the presence of aniline as a permitted adulterant for imported French Rape seed oil; this caused disease in 20,000 people and over 2,500 deaths. The toxic oil syndrome was a multisystemic disease brought on by the ingestion of Rape seed oil denatured with 2% aniline (25-26).

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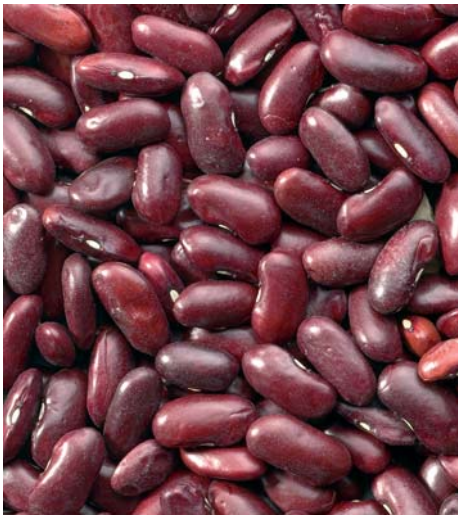
f287 Red kidney bean



Phaseolus vulgaris

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Red kidney bean, Kidney bean, Bean
Source material:	Dried beans
Synonyms:	*P. vulgaris var. humilis*, *P. vulgaris var. mexicanus*
See also:	White bean f15 and Green bean f315

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Allergen Exposure

Geographical distribution

Cultivated in many parts of the world, this firm, medium-sized bean has a dark red skin and cream-coloured flesh. Its popularity can be attributed to its full-bodied flavour. There are many named varieties of the plant, ranging from dwarf forms about 30 cm tall to climbing forms up to 3 m tall.

The seeds of older Green bean pods are known as Red kidney beans, especially when they are dark red. White kidney beans, also referred to as Cannellini beans, do not have the robust flavour of the Red kidney bean.

Environment

Red kidney beans are the main ingredient of chilli con carne, and are also often served with rice. The mature seeds can be canned or dried. They can be boiled, baked, pureed, ground into a powder, or fermented. The seed can also be sprouted and used in salads or cooked. The roasted seeds have been used as a coffee substitute. The green pods may be used as a vegetable. The young leaves can be eaten raw or cooked as a potherb.

The green or dried mature pods, or the seeds alone, are reported to have laxative, diuretic, hypoglycaemic and hypotensive actions. Ground into flour, the seeds are used externally in the treatment of ulcers. The seeds or whole plant may be used as a homeopathic remedy for a variety of diseases.

Haemagglutinin, a lectin, occurs naturally in the Red kidney bean. It is inactivated by thorough cooking of well soaked beans (1).

Unexpected exposure

Red kidney beans are the source of a brown dye, of a fluid for treating used woollen fabrics, and of phaseolin, which has a fungicidal activity.

Allergens

No allergens from this plant have yet been characterised.

An alpha-amylase inhibitor has been detected (2). The allergenicity of this protein is unknown.

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact is not seen frequently (3). In an *in vitro* study, the specific IgE binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked among the extracts of Peanut, Garden pea, Chick pea, and Soybean (4-5).

However, clinical studies have found that there is little cross-reactivity among members of the *Fabaceae* (*Leguminosae*) (6-9).

A study investigated the *in vitro* cross-reactivity of allergens from Mesquite tree pollen (Honey locust tree; *Prosopis juliflora*) and Lima bean (*Phaseolus limensis*/*Phaseolus lunatus*). Of 110 patients with asthma, rhinitis or both, found through intradermal skin determination to be evaluated, 20 were highly positive to Mesquite pollen extract. Of these, 12 patients showed elevated level of IgE antibodies to Mesquite pollen extract alone, and 4 to both Lima bean and pollen extract. Lima bean extract could inhibit IgE binding to Mesquite in a dose-dependent manner. Also, humoral and cellular cross-reactivity was demonstrated (10). Although cross-reactivity was not investigated between Mesquite and Red kidney bean *per se*, cross-reactivity may exist between pollen from this tree and other species of *Phaseolus*.

Clinical Experience

IgE-mediated reactions

Red kidney bean does not commonly induce symptoms of food allergy in sensitised individuals, but as with other legumes, allergic reactions are possible (11).

A study reports on a 33-year-old woman who developed tongue swelling and burning and mouth itching minutes after eating baked Beans. Similar symptoms occurred a day after ingesting Pea soup, and on another occasion within 15 minutes of eating a Bean burrito, and again 20 minutes after eating chilli containing Kidney and Pinto beans. SPT was positive to Red kidney and White bean but negative to Pea, Green and Lima bean. IgE antibodies were detected to Red kidney, White, and Pinto bean, and to Chick pea, Pea and Black-eyed pea (12).

Hand eczema was investigated among 50 caterers and found to be a result of occupation in 47 and endogenous in 3 cases. Contact dermatitis to Red kidney bean, along with skin reactivity, was found in 1 of former group (13).

Other reactions

Red kidney beans contain haemagglutinating lectins, which are toxic (14). Between 1976 and 1989, 50 incidents of suspected Red kidney bean poisoning were reported in the UK. Of these patients, 9 reported the onset of nausea, vomiting and diarrhoea within 1-7 hours of ingestion. The diagnosis was confirmed by the detection of haemagglutinin in the Beans. The diagnosis was made in a further 23 incidents on the basis of symptoms, incubation time and the preparation of beans prior to consumption. In many of the outbreaks reported, the implicated Beans were consumed raw or following an inadequate heating process (1).

The root is dangerously narcotic. Large quantities of the raw mature seed are poisonous. This Bean is a notorious source of flatulence.

Occupational contact dermatitis caused by leaves of the *Phaseolus* plant was reported in a 41-year-old male farmer. Skin lesions appeared soon after he started work on the farm. His main activity was cultivation of Sugar beet, Kidney beans, cereals, Potatoes and Rape. Initially, there were inflamed, scaly patches disseminated over the body. Several years later, a chronic hand eczema appeared. The skin lesions on the body showed a seasonal pattern, with aggravations starting in spring, reaching maximum intensity in summer, and gradually fading in the autumn after the end of field work on the farm. Field work and threshing pods of the Red kidney bean plant in order to recover Kidney beans were activities particularly associated with his skin problems. Approximately 2 to 3 hours after the start of these activities, pruritus appeared, and several hours later erythema of exposed skin appeared, followed by eczema and vesicles. While threshing *Phaseolus* pods, the patient also experienced dyspnoea. SPT with the leaf was negative, but positive with patch tests (15).

f287 Red kidney bean

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Oryza sativa

Family: *Poaceae* (*Gramineae*)

Common names: Rice, Jasmine rice, Wild rice, Basmati rice, popped Rice, Rice semolina

Source material: Unpolished rice

All Rice grown in the United States and most of that cultivated in other countries is of the species *Oryza sativa L*. Some 20 to 25 species of *Oryza* are known. The species *O. glaberrinia Steud*. is cultivated in Africa

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Allergen Exposure

Geographical distribution

Rice is an erect annual grass, up to 1.2 m tall, producing tiny oblong grains (28,000 to 44,000 per kg, depending on the variety). The hard, starchy kernel is the part eaten; this is surrounded by a series of bran coats (rich in vitamins and minerals) and a rough outer, inedible hull. Native to the tropics and subtropics of Southeast Asia (where it was cultivated since at least 5000 B.C.), Rice is now grown in many localities throughout the world with favourable climatic conditions. More than 90% of the world Rice production is in Asia, China and India being the largest producers.

Rice is a staple for almost half the world's population. The 8,000-plus varieties of Rice are grown in 2 ways. Aquatic Rice (paddy-grown) is cultivated in flooded fields. The lower-yielding, lower-quality hill-grown Rice can be grown on almost any tropical or subtropical terrain. Rice is also classified by size and shape, as long-, medium- or short-grain, and by colour, as white (with the husk, bran and germ removed) or brown (with only the inedible husk removed). Many methods of milling, polishing, parboiling, etc., are employed in different cultures, resulting in many different forms and nutrient values of the final product. Among these forms are regular milled white Rice, instant/pre-cooked Rice, jasmine, wild, basmati, and popped Rice, and Rice semolina, aka Rice flour.

Environment

Rice is used in a great variety of dishes, often as a base for meat or vegetables. Specialised ethnic dishes include Italian risotto and Japanese sushi.

Rice that is rich in starch is used extensively as breakfast food - as puffed Rice, flakes, or Rice crispies. Starchy types of Rice are also used in pastries, soups, and starch pastes; glutinous types, containing a sugary material instead of starch, are used in the Orient in candies and for other special purposes. Rice is important in the manufacture of alcoholic beverages. Rice flour is used in various mixes.

Rice is a good source of carbohydrate; brown Rice provides the same energy as white, but contains more vitamins and minerals. Rice bran, the grain's outer layer, is high in soluble fibre and is effective in lowering cholesterol. Enriched or converted Rice contains calcium, iron and many B-complex vitamins, with brown Rice being slightly richer in all the nutrients.

All parts of the plant, and even the water from soaking or cooking Rice, and the lye from charred stems, figure in folk medicine, in a great variety of uses. B vitamin-rich unpolished Rice is a preventative and treatment of beriberi.

Unexpected exposure

See under Environment. Rice hulls (bran) are used for animal fodder, fuel, insulation, and in certain manufacturing processes such as the production of purified alpha cellulose and furfural. Rice straw is used as roofing and packing material, animal feed, fertiliser, fabric, and fuel.

Allergens

In Rice allergy, proteins with molecular masses of 14-16, 26, 33, and 56 kDa have been demonstrated to be potentially allergenic. The 33 kDa allergen was identified as a novel type of plant glyoxalase I that is expressed in various plant tissues, including maturing seeds. (1) The majority of the allergic components are albumins with molecular weights between 14 and 16 kDa (2). The 16 kDa Rice protein has been reported to be a major allergen and responsible for cross-allergenicity between cereal grains in the *Poaceae* family (3). A 19 kDa globulin protein has also been isolated (4).

Other allergens partially characterised have been designated RAP, RAG 1, RAG 2, RAG 5, RAG 14, and RAG 17. RAG 17 is a 16 kDa protein, a member of the alpha-amylase/trypsin inhibitor protein family (5-6). Although raw Rice is more allergenic than cooked, some of the allergens are probably heat-stable and resist proteolysis (7).

In a more recent study that evaluated Rice allergy in Indian patients, in sera of individuals allergic to Rice, 14-16, 33, 56 and 60 kDa proteins were shown to be major IgE-binding components in Rice. Boiled Rice retained 4 IgE-reactive proteins of 16, 23, 33 and 53 kDa (8).

The following allergens have been characterised:

Ory s LTP, a 14 kDa lipid transfer protein. (9-13).

Ory s aA/TI, a 16 kDa alpha-amylase/trypsin inhibitor. (5-6,14-20).

Ory s Glyoxalase I, a glyoxalase (1,3,12,21).

Ory s 12, a profilin (22-23).

Ory s 1, Ory s 2, Ory s 3, Ory s 7, Ory s 11, Ory s 12 and Ory s 13 have been characterised in Rice pollen and contribute to asthma, allergic rhinitis and allergic conjunctivitis as a result from exposure to Rice pollen. Ory s 12, a profilin, has been detected in both Rice seed and Rice pollen (22,24).

Rice also contains a lipid transfer protein (9 10). LPTs are heat-stable proteins and may play a role in allergy to cooked Rice. A report was made of 3 individuals who developed rhinoconjunctivitis and asthma as a result of exposure to the lipid transfer protein of raw Rice thrown at weddings, but who could tolerate cooked Rice. This may indicate some modification of Rice lipid transfer protein during cooking (12).

At least 5 alpha-amylase/trypsin inhibitors have been isolated from Rice, including Ory s aA/TI. Patients may react with all 5 proteins, whereas others specifically react with individual proteins only (16). This family of allergens is highly resistant to digestive enzymes (20) and is heat-stable (6). There is a suggestion that some epitopes of recombinant versions of these proteins are still immunoreactive when they are expressed as their fragments (18).

Although Rice seed contains the panallergen profilin, the levels of this are much lower than those in foods commonly known to contain profilin, *e.g.*, Celery (22).

A chitinase has been isolated from Rice. The substance accumulates to a high level in the roots of the plant, but only low levels are found in stem and leaf tissue (25). Whether the chitinase is found in the seed, and whether this chitinase has allergenic potential, are questions that have not yet been evaluated.

Potential cross-reactivity

An extensive cross-reactivity among pollen of the different individual species and tribes of the *Poaceae* family could be expected and in fact does occur frequently. (26) Although similar patterns of cross-reactivity may occur among the seeds/grains of the family, this has not been as well determined as in the case of pollen. *In vitro* cross-reactivity has been demonstrated among IgE binding proteins of Corn, Rice, Soybean and Peanut. A high degree of cross-reactivity between Rice and Corn was thought to be due to the fact that they both belong to the same botanical family. The authors state that the clinical significance of these cross-reactivities is not yet known and that clinical studies will be required to put these findings into perspective (27).

Cross-allergenicity among the cereal grains Rice, Wheat, Corn, Japanese Millet and Italian Millet was examined by RAST inhibition assay, and significant close correlations in every combination of IgE antibody values for the 5 grain extracts were found (3).

Allergens of 14 and 18 kDa have been isolated from Buckwheat and shown to be major proteins. These were found to share some homology with Rice proteins associated with Rice allergy, and cross-allergenicity with Buckwheat proteins was postulated (28). However, some Buckwheat-allergic subjects do not develop immediate adverse reactions after ingesting Buckwheat, despite high levels of Buckwheat-specific IgE antibodies. Further investigation has led to the conclusion that there is IgE antibody cross-reactivity between Buckwheat and Rice, and that IgE antibodies from immediate hypersensitivity reaction-negative subjects might recognise the epitopes on Buckwheat antigens that cross-react with Rice antigens, whereas IgE antibodies from immediate hypersensitivity reaction-positive subjects might bind to Buckwheat-specific epitopes (29-30). Thus, in spite of cross-allergenicity between Buckwheat and Rice, Rice ingestion only uncommonly induces immediate hypersensitivity reactions, even in subjects with high IgE for Rice; this is not the case for Buckwheat-induced immediate hypersensitivity reactions (31).

Approximately 86% of Maize-allergic patients were shown to have allergen-specific IgE to a 9 kDa protein, shown to be a lipid transfer protein. Immunoblotting inhibition showed that this LTP cross-reacts completely with Rice and Peach LTPs but not with Wheat or Barley LTPs. A 16 kDa allergen was also isolated (recognised by 36% of patients) and shown to be the Maize inhibitor of trypsin. This protein cross-reacts completely with grass, Wheat, Barley, and Rice trypsin inhibitors (2,32). Other studies have confirmed the high degree of cross-reactivity between Rice and LTPs from other foods (10). Cross-reactivity has been demonstrated between Rice lipid transfer protein and those from Peach and Apple (11). The 3-dimensional structure of Rice lipid transfer protein closely resembles the published structures of Wheat, Barley and Maize LTPs (13).

Clinical Experience

IgE-mediated reactions

Rice may uncommonly induce symptoms of food allergy, asthma, rhinitis, eczema and urticaria in sensitised individuals; however, in communities where Rice is a staple food, *e.g.*, in the Far East, reactions may be more frequently encountered (33-40). With the increase of Rice consumption in the West, the prevalence of allergy to Rice may increase. Symptoms reported in Rice-allergic individuals include abdominal cramping and similar pain, nausea, vomiting, rhinitis, rhinoconjunctivitis, dyspnoea, asthma, contact urticaria, atopic dermatitis, dermatitis, angioedema and anaphylaxis. Individuals may be sensitised without being symptomatic (41-43). A high percentage of this sensitisation may be of this kind (9).

In 148 Malaysian adults with symptoms of nasal congestion and rhinorrhoea and 113 control subjects without rhinitis symptoms, SPT evaluation of 11 foods common in the Malaysian diet showed that 48% of the patients with rhinitis had skin reactivity to food, compared with 4.4% of control subjects. The most commonly implicated foods were Shrimp (48%) and Rice (30%), both of which are common in the Malaysian diet (34).

f9 Rice

In a study that evaluated Rice allergy in Indian patients, of 1,200 patients screened, 165 presented with a history of Rice allergy, and of these, 20 (12.1%) demonstrated marked skin reactivity and 13 showed significantly raised IgE antibodies to Rice. DBPCFC confirmed Rice allergy in 6/10 patients. The authors concluded that IgE-mediated Rice allergy affects approximately 0.8% of Indians with asthma and rhinitis (8).

Rhinoconjunctivitis, asthma and contact urticaria from handling Rice and other cereals were reported in a housewife. She tolerated cooked cereals. SPT with a Rice extract and cutaneous challenge with raw Rice were positive. Raw Rice produced immediate and late clinical effects, and objective lung function tests confirmed the symptoms of asthma (44). Other studies have also reported Rice-induced asthma in adults (45-46). The allergen-specific IgE level may be raised in these individuals (46). In addition, a high frequency of food hypersensitivity may occur in individuals with allergic rhinoconjunctivitis (47).

A 9-year-old girl seen during a follow-up visit for asthma (perennial symptoms) reported that she "disliked" foods with Rice and had avoided eating them for the last 3 years. Attempts to feed her with Rice had resulted in immediate nausea, abdominal pain and diarrhoea. On one occasion, she had suffered urticaria-angioedema in the kitchen while her mother was sorting Rice. She had previously been found allergic to grass pollens through intradermal but not epidermal tests. Skin prick tests and prick-prick tests with various cereals, including Rice, Wheat, Barley, Oat and Lentil, demonstrated a marked wheal and flare reaction only to Rice with both tests. Total IgE was 165 kU/l, and Rice-specific IgE was 13.2 kU_A/l. A double-blind, placebo-controlled food challenge resulted in nausea, abdominal pain and diarrhoea within 10 minutes of ingestion. She had no problems when eating other cereals. She therefore demonstrated allergy to the ingestion of cooked Rice and to inhalation of raw Rice proteins (48).

Rice thrown at weddings may result in rhinoconjunctivitis and asthma. Three patients are described who experienced asthma or rhinoconjunctivitis to raw Rice by inhalation of Rice dust at these events. All were able to tolerate Rice by ingestion, but were allergic to Peach. IgE antibodies to Rice and Peach were detected in all 3 patients. Recombinant Pru p 3, as well as Rice seed lipid transfer protein, bound IgE from sera of 2 patients whose sera were available for testing. SPT was positive for natural Pru p 3. The authors suggest that, as lipid transfer proteins are purported to be heat-stable, the fact that these patients could tolerate cooked Rice may indicate some modification of Rice lipid transfer protein during cooking (12).

Anaphalaxis and anaphalactoid reactions have also been reported in adults and children (49-50). Food-dependant exercise-induced anaphylaxis (FDEIA) may occur (51), as well as FDEIA related to multiple food intake (52). The observed recurrence of FDEIA following intervention may be a result of concomitant ingestion of other foods such as Rice and Peanut (53). Anaphylaxis has also been reported to the inhalation of Rice dust (54).

Allergy to Rice dust was also reported in 2 children. A 7-year-old girl with asthma was able to eat cooked Rice, but she was found to have IgE antibodies to Rice of 38.3 kU_A/l. It was thought that her asthma was exacerbated by Rice powder inhalation, as the family milled Rice. Her symptoms improved greatly when she was away from the business. The second patient, a 3-year old boy with atopic dermatitis whose family brewed sake (made from Rice), was shown to have allergen-specific IgE of 2.21 kU_A/l to Rice. The dermatitis improved when Rice was removed from his diet, but a flare occurred once when he came near Rice-threshing or milling machinery (55).

Three individuals who experienced severe allergic reactions to Rice, including anaphylaxis, were reported. The severity of the allergic response was related to the presence of the lipid transfer protein allergen in Rice. A 50-year-old woman with a history of grass pollen hypersensitivity and oral

itching following the ingestion of many kinds of fruits and tree nuts experienced generalised urticaria and angioedema associated with dyspnoea about 30 minutes after eating a "risotto" dish (boiled Rice with mushrooms), and about 2 months later she experienced oral allergy syndrome followed by generalised urticaria and collapse following the ingestion of a risotto with saffron. A 25-year-old woman with grass pollen allergy and oral allergy to a number of fruits and nuts had experienced generalised urticaria and angioedema associated with dyspnoea about 1 hour after eating a risotto dish (boiled Rice with saffron). A 30-year-old man with a history of grass pollen allergy, and oral itching following the ingestion of fruits and nuts, experienced several urticaria reactions following the ingestion of risotto dishes (Rice with Chicory) and Onion. *In vitro* inhibition studies using lipid transfer protein purified from both Rice and Apple, as well as whole Peach extract, demonstrated that the lipid transfer protein was the relevant allergen in these patients, and demonstrated cross-reactivity between Rice lipid transfer protein and those from Peach and Apple (11).

Children may also develop allergy to Rice, although anaphylaxis appears to be uncommon. Three admissions of a 6-month-old girl due to the sudden onset of respiratory and gastrointestinal symptoms, paleness and a reduced level of consciousness following ingestion of Rice flour have been reported. A provocation test resulted in an anaphylactic reaction (56). A similar report of anaphylaxis to Rice flour in a 6-month-old girl has been documented (57).

The effect of Rice allergy on the skin has been documented by many studies. In 200 of 226 patients (90.5%) with atopic dermatitis visiting a Japanese hospital, oral food challenge tests showed that food allergy was involved, and Rice allergy affected 2.5% (58). In a study of 1006 Japanese patients with typical and atypical lesions of atopic dermatitis, who were analysed statistically by correlating the clinical severity to serum IgE antibody values, the suggestion was supported that Rice allergy strongly contributed to the development of the severity of this condition. Of 25 patients with severe atopic dermatitis and a IgE antibodies to Rice who were treated by a Rice exclusion diet, 9 were remarkably improved, 10 were moderately improved, and no effect was seen in 6 (37). The results of a study suggested that ocular-type atopic dermatitis belongs to the most severe end of the spectrum of atopic dermatitis, and that Rice and Wheat may contribute to the pathogenesis of severe atopic dermatitis, resulting in ocular complications (47,59).

Based on a statistical analysis of the correlation between Rice-specific IgE score and clinical severity in atopic dermatitis patients, the probable involvement of Rice allergy in many severe cases was postulated (60-61).

Contact urticaria from Rice has also been reported (62). Similar allergic effects were recorded in a 17-year-old female presenting with acute erythema of the hands, oedema of the eyelids, dyspnoea and cough following contact with raw Rice, which occurred from throwing raw Rice during a wedding. She was able to tolerate cooked Rice by ingestion. The authors suggested that the adverse respiratory and skin reactions resulted from Rice dust (63). Further insight into this condition comes from a report on a 30-year-old man with atopic dermatitis who experienced erythema, itching and urticarial erythema of the hands several minutes after washing Rice in water, though he had always eaten cooked Rice without problems. SPT with water used to wash regular Rice was markedly positive, but only mildly positive with water used to wash allergen-reduced Rice. Total serum IgE was 4,200 kU/l, and serum Rice-specific IgE was reported as class 2. Immunoblotting analysis of 3 atopic dermatitis patients with high IgE antibody levels to Rice detected several polypeptides, but none for this patient. The authors concluded that these findings suggest that the allergen responsible for contact urticaria in this patient might be water-soluble, heat-unstable, and not contained in allergen-reduced Rice (61).

Occupational contact dermatitis and/or asthma may occur in Rice workers and occasionally in bakers (64,66).

Other reactions

Food protein-induced enterocolitis syndrome, a symptom complex of severe vomiting and diarrhoea occurring in infants several hours after the ingestion of particular food proteins, has been reported to be caused by Rice in some instances (67). Although food-sensitive enteropathy is more often caused by milk, Rice and ground Rice may also temporarily damage the small intestinal mucosa in infancy (68-69). Reactions may be severe. Shock, nausea, vomiting, and diarrhoea have been reported in 4 infants. Occult blood in stools of these infants was positive. All immunologic tests were negative. Nevertheless, the authors conclude that, based on the clinical findings in these patients, the adverse effects were probably allergic in nature (70).

Red yield rice (Cholestin) is produced from the fermentation of Rice with the mould Monascus purpureus went, a traditional oriental food commonly known as Hongqu in China and as Red yeast rice in the United States and said to have health-enhancing qualities. A 26-year-old butcher was investigated following a severe anaphylactic episode, with sneezing, rhinitis, conjunctivitis, and generalised pruritus followed by widespread urticaria, angioedema and dyspnoea, after preparing sausages containing Red yield rice (71). Although uncommon, anaphylaxis to Red yield rice has been reported in other studies (72).

A distinct clinical syndrome seems to be associated with exposure to Rice husk dust. The manifestations of this “Rice millers' syndrome” include acute and chronic irritant effects on the eyes, skin, and upper respiratory tract; and allergic-like responses such as rhinitis, dyspnoea, bronchospasm, and eosinophilia. Radiological opacities in the chest, probably representing early silicosis or extrinsic allergic alveolitis, have been reported (73). Similarly, findings suggesting increased asthma prevalence among California Rice farmers and workers have been reported. Radiologic findings were consistent with dust or fibre exposure, although no association with specific farming activities was identified (74).

Individuals working with Rice may in fact be allergic to Rice pollen and not Rice *per se* (75). Among 260 Costa Rican patients with asthma and 100 non-atopic subjects studied with skin prick tests for all *Poaceae* tribes, 51.2% were positive to at least 1 tribe. The pollen of the *Oryzeae* tribe (Rice) showed the highest positivity among asthma patients of the province producing most of the country's grains (76-77).

Contact dermatitis from Rice leaf has been reported (78).

Talc-coated Rice (clearly labelled as such) is available only in a few markets, usually those specialising in South American foods. It must be thoroughly rinsed before cooking, as the talc can be contaminated with asbestos.

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f5 Rye

Secale cereale

Family: *Poaceae* (*Gramineae*)

Common names: Rye, Rogge

Source material: Untreated planting seeds

See also: Cultivated rye g12

There is a need to differentiate between Rye the foodstuff (*Secale cereale*), Cultivated Rye grass pollen (*Secale cereale*) g12, Rye grass pollen (*Lolium perenne*) g5, and Wild Rye grass pollen (*Elymus tricoides*) g70. This distantly related genus, *Elymus*, contains species known as Wild Ryes, which are used as cover and for forage. A Wheat hybrid is known as Giant Rye

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Allergen Exposure

Geographical distribution

Rye, a hardy, tufted annual grass 1-1.5 m tall, was probably native to south-western Asia but is now widely cultivated in the temperate regions of the world (often where conditions are unfavourable for Wheat), where it is used mostly as a bread grain and as a livestock feed. It is grown especially extensively in northern Europe and Asia. It apparently co-evolved with Wheat and Barley for over 2,000 years until its value for food was recognised. But it has many other uses. Rye is taller but similar in habit to Wheat, reaching 0.5 to 1.2 m, with a nodding, longer, more slender, somewhat terminal spike.

Less than 50% of the Rye grown in the U.S. is harvested for grain, with the remainder used as pasture, hay, silage or as a cover crop. About half of the amount harvested for grain is used for livestock feed or exported, and the remainder is used for alcoholic beverages, food, and seed.

Environment

Rye is used in bread making, alcoholic fermentation, and as feed for livestock. The straw may be useful for thatching.

The grain is used to make flour, the importance of which is second only to Wheat flour. Although Rye flour does not develop true gluten, it has proteins that give it the capacity for making leavened bread; which is, however, denser and usually darker than Wheat bread. Rye is usually mixed with 25 to 50% Wheat flour for bread making. Rye bread is especially popular in northern Europe. Rye can also be used to make cakes, etc. The seed can be sprouted and added to salads. The roasted grains are a substitute for coffee.

Malt, a sweet substance produced by germinating the seed, is extracted from the roasted germinated seed and used as a sweetening agent and in making beer, etc. Canadian and United States whiskies are made mainly from Rye.

The grains are used in folk remedies for tumours and other cancers. They are reported to be laxative.

Unexpected exposure

See under Environment. The straw is used as a fuel; for thatching, paper-making, weaving hats, mats, etc.; as a packing material for nursery stock, bricks and tiles;

for bedding, paper manufacture, archery targets, and mushroom compost. Rye flour is frequently used in the wood industry to increase the viscosity of the glue employed to manufacture boards (1).

Allergens

The following allergens have been isolated:

Sec c 12, a profilin (2).

Sec c 20, a secalin (3-7).

Sec c a A TI, a 13.5 kDa alpha-amylases/ trypsin inhibitor (8-10).

Sec c 1, Sec c 2, Sec c 4, Sec c 5, Sec c 12 and Sec c 13 have been characterised in Cultivated rye grass pollen and contribute to asthma, allergic rhinitis and allergic conjunctivitis from exposure to this pollen. Sec c 12, a profilin, has been detected in both Rye seed and Cultivated rye pollen (1). See Cultivated rye grass g12.

Rye seed contains the panallergen profilin, but at much lower levels than found in Rye pollen and in other foods such as Celery or Tomato (1), and may be of low clinical significance, as heat processing will destroy the protein. Nonetheless, profilin in Rye seed may play a role in occupational asthma, caused by bakers inhaling Rye flour or dust.

Various other allergenic proteins have been detected but not characterised.

Using IgE-immunoblotting analysis and serum samples from 40 adult patients with allergy to cereals (35 patients with atopic dermatitis, 1 with rhinitis and 4 with urticaria), polyspecific binding patterns were demonstrated with each cereal; Rye exhibited 35 bands. The most common protein binding to patients' sera (16/35, 46%) was a 40 kDa protein. There were 16 similar proteins detected in Wheat, Rye and Barley extracts, suggesting cross-reactivity among these cereals (11). Rye flour proteins of 21 and 12 kDa have been identified as major allergens in serum from Wheat-hypersensitive individuals (12).

The major Wheat allergen associated with exercise-induced anaphylaxis is an omega-5 gliadin. Similar allergens have been detected in Rye. Through SPT with these allergens in Rye, gamma-70 secalin was detected in 10/15 (67%) of patients, to gamma-35 secalin in 3/15 (20%) patients, and to gamma-3 hordein in 7/15 (47%) patients (3).

The salt-soluble proteins of Wheat and Rye flour dust are considered the most relevant allergens in Baker's asthma (9,13). Members of the cereal alpha-amylase/trypsin inhibitor family are main allergens involved in allergic reactions to cereal flours. However, different allergenic behaviours were found among homologous allergens from Rye, Barley, and Wheat (7-8). Three Rye proteins, namely Sec c 1, RDAI-1 and RDAI-3, were shown to provoke positive SPT in more than 50% of Rye-allergic patients, although the serum IgE antibody levels were lower (7-8). Franken *et al*. isolated 2 allergens with molecular weights of 35 and 14 kDa in water-soluble Rye flour extracts using immunoblotting techniques on sera from 100 bakers (14). Garcia-Casado *et al*. isolated a protein of about 13.5 kDa from Rye flour. This allergen may be the same as the 14 kDa allergen isolated by Franken *et al*. This protein provoked positive skin-specific IgE responses in 15/21 (71%) patients with Baker's asthma (9).

In 2 bakery workers with baker's asthma caused mainly by exposure to Rye flour, Rye flour immunoblotting showed IgE-binding bands of around 12-15 kDa that correspond to Rye flour enzymatic inhibitors and that were not present in the Wheat flour immunoblot (15).

In a report describing occupational allergy to Rye flour in 9 wood workers who were exposed to wood dust and experienced asthma and/or rhinoconjuncitivis, implicated allergens were 3 purified Rye allergens belonging to the cereal alpha-amylase inhibitor family, and in particular Sec c 1 (8/9 patients) (1). These inhibitors, as well as their Wheat and Barley homologues, have been identified as prominent allergens associated with baker's asthma (10).

Six distinct gamma- and omega-type secalins, together with 2 low-molecular-mass glycoproteins, have been identified as the major coeliac immunoreactive proteins from

Rye endosperm. A group of secalins has been isolated: an omega-type secalin of 40 kDa (omega 1-40); 3 gamma-type secalins, a 70 kDa (gamma-70), 2 35 kDa (gamma-35) proteins, and 2 low-molecular-mass glycoproteins of 15 and 18 kDa. These proteins are also involved in non-IgE mediated coeliac disease (4). It appears that the presence of IgA and IgG antibodies to different cereal antigens is a result of natural exposure and in atopic dermatitis displays little diagnostic significance, in contrast to antigliadin antibody response in dermatitis herpetiformis and coeliac disease (16).

Class I and class II chitinases have been isolated from Rye seed. The chitinase accumulates in the seed during the later stage of development. The allergenic potential was not evaluated (17-18).

Antifreeze proteins, which are proteins that have the ability to retard ice crystal growth, have been identified as the most abundant apoplastic proteins in cold-acclimated winter Rye leaves. All tests indicated that these antifreeze proteins are similar to members of 3 classes of pathogenesis-related proteins, namely, endochitinases, endo-beta-1,3-glucanases, and thaumatin-like proteins (19).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (20). By using RAST inhibition tests, cross-antigenicity was shown to exist between different cereal grains: Rye, Wheat, Triticale, Barley, Oat, Maize and Rice. The degree of cross-reactivity closely paralleled their taxonomic relationship and appeared to be in the following order of decreasing closeness: Wheat, Triticale, Rye, Barley, Oat, Rice and Maize. The allergenic activity in the Rye and Wheat extracts was found to be distributed among various fractions of different molecular weights (21). Other studies have documented cross-reactivity between Rye and Wheat (22), and Rice may cross-react with Rye, Maize, Wheat and Rye pollen (23). Cross-reactivity between Rye and Rye pollen has been shown, as they both contain the Sec c 1 (b) allergen (7-8). Cross-reactivity has also been demonstrated among grain extracts of Wheat, Rye, Barley and Oats. The results of the study suggested that the bran layers of cereal grains are at least as allergenic as the flour derived from the grain (24).

A number of Wheat and Barley flour proteins that belong to the cereal alpha-amylase/trypsin inhibitor family have been identified as major allergens associated with baker's asthma. Members of the Rye alpha-amylase inhibitor family are main allergens involved in allergic reactions to cereal flours. In a study comparing the allergenic potential among the homologous allergens from Rye, Barley, and Wheat, different degrees of allergenicity were shown among the components in Rye, as compared with the Wheat and Barley homologues (7-8). IgE antibody studies have also shown a strong association between the levels of allergen-specific IgE to Wheat flour and those to Rye and Barley flour, and cross-reacting proteins could be demonstrated using competitive RAST inhibition studies (11). The existence of cross-reacting proteins between Barley, Rye and Wheat flour extracts, as well as among the pollens of cereals and cereal flours, has been reported (25).

The major Wheat allergen associated with exercise-induced anaphylaxis is an omega-5 gliadin, and similar allergens have been detected in Rye. The gamma-70 and gamma-35 secalins in Rye and the gamma-3 hordein in Barley were shown to cross-react with omega-5 gliadin, a major allergen in Wheat-dependent, exercise-induced anaphylaxis, suggesting that Rye and Barley may also elicit symptoms in patients with Wheat-dependent, exercise-induced anaphylaxis (3).

Allergy to Kiwi, Poppy seed, and/or Sesame seed often occurs in patients with a simultaneous sensitisation to nuts and flour. In a study characterising these cross-reactivities, the degree of cross-reactivity among Kiwi, Sesame seeds, Poppy seeds, Hazel nuts, and Rye grain was found to be very high in these patients. The existence of both cross-reacting and unique components was observed; however, the authors report that the cross-reacting and unique components could be different for different patients (26).

Papain has been reported to cross-react with Bromelain, Wheat flour, Rye flour, Grass pollen and Birch pollen (27).

In a Polish study investigating the relationship between hypersensitivity in 944 children to grass pollens and to Wheat, Rye and Soya, a very high correlation between hypersensitivity to grass and the presence of IgE antibodies to Wheat, Rye and Soya was found (28).

Clinical Experience

IgE-mediated reactions

Rye and Rye flour may commonly induce symptoms of food allergy in sensitised individuals, in particular in bakers. Symptoms may include asthma, rhinitis, sneezing and wheezing. Food allergy with gastrointestinal symptoms, including nausea, vomiting, gastric irritation, abdominal pain and diarrhoea, has been reported. Cutaneous symptoms may include pruritis, urticaria, dermatitis, atopic dermatitis and angioedema. Anaphylaxis or vascular collapse with exercise has been documented (29-33).

In a Polish study utilising SPT for food allergens in 270 pollen-allergic patients, the most prevalent allergens were found to be to nuts, Celery, Rye flour, Carrot, Strawberry, Pork and beans (28). Oral provocation tests have also shown the relevance of Rye as a food allergen. Allergen-specific IgE and histamine-release tests were employed to evaluate patients with immediate hypersensitivity. Patients with delayed hypersensitivity underwent patch or lymphocyte-proliferation tests (32). In an evaluation of sensitisation to cereal in 40 children, the most important allergen was Wheat, followed by Barley and Rye (34).

Anaphylaxis with exercise following the ingestion of Rye has been reported (31), as well as exercise-triggered recurrent anaphylaxis or urticaria as a result of allergy to gliadin (found in Wheat, Rye, Barley and Oats) (35). A study has suggested that Rye and Barley may also elicit symptoms in patients with Wheat-dependent, exercise-induced anaphylaxis (3).

Eosinophilic esophagitis (EE) is often associated with concomitant atopic diseases; in children with EE, for whom food allergens have been identified as causative factors, elemental and elimination diets result in an improvement or resolution of symptoms. However, among adults, most patients are sensitised to aeroallergens (most commonly to grass pollen and cereals), which may cross-react with plant-derived food allergens. Six adults with permanently active eosinophilic esophagitis, who were sensitised to grass pollen and the cereals Wheat and Rye, underwent a double-blind placebo-controlled food challenge and were kept on an elimination diet, avoiding Wheat and Rye for 6 weeks. However, the challenge tests with Wheat and Rye did not provoke any symptoms of eosinophilic esophagitis in any, and the elimination diet failed in reducing disease activity. One patient noted an improvement of symptoms, but endoscopic and histopathologic findings were unchanged (36).

Occupational allergy to Rye exposure may occur in animal feed and husbandry workers, bakers and other employees in bakeries, other food industry workers, and wood workers.

Baker's asthma is the most frequent occupational lung disease in Switzerland and West Germany. Cereal flours, and more rarely flour parasites, are implicated as the responsible allergens. In a study of 31 patients with Baker's asthma, approximately 74% and 61% were found to have IgE antibodies to Wheat and to Rye flour respectively (37). Other studies have reported similar findings: bakers with workplace-related respiratory symptoms showed sensitisation to Wheat flour (64%), Rye flour (52%), Soya bean flour (25%), and alpha-amylase (21%) (38). Asthma has been reported following exposure to cereal flour contained in animal formula feeds (39).

Rye and Rye flour may also cause occupational rhinitis and dermatitis, as reported in studies conducted on bakers and pastry cooks (40-42). Allergy to Rye flour has been reported in bakers (43-44). Occupational protein contact dermatitis may result from contact with Rye (45).

Two bakery workers with baker's asthma and rhinoconjunctivitis, caused mainly by exposure to Rye flour, were described. Specific inhalation challenge with Wheat flour did not elicit an asthmatic reaction; however, both patients showed an early asthmatic reaction to a Rye flour challenge (14). Similarly, a baker with asthma reported a workplace response to Rye flour but none to Wheat flour, despite co-reactivity to both Wheat and Rye antigens. SPT, IgE antibody determination and basophil stimulation tests were positive for both Wheat and Rye antigen, but quantitatively greater for Rye than for Wheat. Bronchial challenge elicited a much greater response to the Rye-Wheat flour mix used in the bakery than to 100% Wheat flour. The authors concluded that the greater clinical response to Rye than to Wheat may be immunologically mediated, but could have also been due to the physical characteristics of Rye flour, such as the larger dose of inhaled airborne particles or an irritative effect (46).

In a South African study of 517 supermarket bakery workers, a quarter (27%) of bakers had skin reactivity to cereal flours or additives, with the most common sensitisers being cereal flours such as Wheat and Rye (16%) and the least common being Alpha-amylase (3%). A higher proportion had elevated IgE antibody levels to Wheat (26%), Rye (24%) and Alpha-amylase (4%) (47). In individuals with baker's asthma, immediate asthmatic reactions may occur, or there may be dual reactions consisting of an immediate reaction followed by late reactions after some hours (48).

In a Korean study evaluating the IgE sensitisation rate and cross-reactivity in an agricultural setting, of 5,340 patients complaining of various allergic diseases and visiting a Korean allergy clinic, the sensitisation rate to Rye grain was 9.5%. Buckwheat and Soybean were the most prevalent allergens (49).

Cereal flours are used in the wood industry to improve the quality of the glues necessary to produce veneer panels. Three individuals were found to be allergic to cereal alpha-amylase inhibitors, which are important occupational allergens responsible for baker's asthma, and which are members of the alpha-amylase inhibitor family, allergenic proteins found in Rye, Barley and Wheat (50).

Occupational allergy to Rye flour was reported in 9 wood workers who were exposed to wood dust and experienced asthma and/or rhinoconjuncitivis. They worked as carpenters or sawmill operators. The adverse reactions appeared to be caused by the Rye flour used in the manufacture of agglomerate boards. SPT for a range of wood dust extracts was negative in 7 of the 9. One individual was shown to have positive SPT to Western red cedar and ramin, and another to Western red cedar and iroko. In contrast, all subjects were shown to have skin reactivity to Rye. (A commercial Rye flour extract was used both in the skin and in the conjunctival tests.) Five were positive on bronchial challenge tests (1).

Other reactions

Rye contains a gluten-complex protein which may result in coeliac disease (coeliac enteropathy) in genetically susceptible individuals. (51) Although the prevalence of coeliac disease is high in northern Europe, differences among countries exist. Among 771 children (381 Swedish and 390 Danish) investigated for suspected coeliac disease (CD), only 24 CD patients were found among the Danish children, compared with 155 in the Swedish group, despite the closely related ethnic, geographical, and cultural background of the two populations. The difference was attributed to a difference in the amount of gluten-containing Rye flour eaten. The Danish infant diet differed significantly from the Swedish one in containing a larger amount of the lower-gluten Rye flour (52).

Vasospasm related to ergot intoxication has been recognised since the Middle Ages, when it occurred due to ingestion of Rye contaminated with the mould Claviceps purpurea. Today ergotism is a rare cause of peripheral ischaemia, most often associated with ergotamine tartrate therapy for migraine headaches (53). Nevertheless, an awareness of this condition is important, as cases of ergotism may still occur. A 42-year-

old farmer afflicted for 6 months with increasing pain in both feet and calves was reported. Angiography demonstrated progressive narrowing of all lower-leg arteries. There were no palpable pulses in the right foot, and those in the left foot were markedly reduced. The patient had been exposed by inhalation to ergotamine-containing milling dust in the preparation of Rye flour. A high plasma ergotamine level was documented. Chronic ergotamine inhalation can cause ergotism affecting peripheral arteries (54).

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f10 Sesame seed

Sesamum indicum

Family: *Pedaliaceae*

Common names: Sesame seed, Sesame, Benne seed

Source material: Unpolished seeds

Other species of Sesame include *S. indicum*, *S. radiatum*, *S. schum*, and *S. thoron*

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Allergen Exposure

Geographical distribution

The *Pedaliaceae* family contains 18 or more species, most of them indigenous to Africa and Asia. *Sesamum indicum*, originally from India, is now grown very widely: in India, the Middle East, the United States, Latin America, China, and elsewhere. It is a perennial herbaceous plant that grows up to 1 metre high. Its flowers are pink or light blue (1).

Sesame may be the first seasoning ever used. The Chinese burned Sesame oil for light and to make soot for their ink blocks. African slaves brought Sesame seeds to America. The Japanese use Sesame seed as a health food and lead the world in Sesame seed imports, followed by Europe and the US.

The fruit is a small capsule containing many seeds, which are black, white, yellow or red. They are used in food either unprocessed or after hulling. Sesame seeds are used crushed, for their oil, and as cakes (the solid residue left after processing of the oil). About 70% of the world's Sesame seed is processed into oil and meal.

Environment

The seed is available packaged in supermarkets and can be found in bulk in Middle Eastern markets and health food stores. Sesame seeds often feature in candies and baked goods, and are a common ingredient in savoury dishes of ethnic cuisines. A special process produces a clear white seed that is common on hamburger buns.

The seed can also be ground and used as flour, or as butter, known as “tahini”. It can also be fermented into “tempeh”, or ground into a powder and mixed with a sweetener to make “halva”. The seeds can also be sprouted and used in salads. Edible oil is obtained from the seed. It is used for cooking, in margarines, and so on.

Sesame seed is rich in unsaturated fatty acids, calcium, protein, and vitamins A, B and E.

Sesame has bactericidal activities, and it also acts as an antioxidant that can inhibit the production and absorption of cholesterol. It is believed to help prevent and/or combat cancer and heart disease and to have anti-diabetic, anti-ulcer and laxative properties. The lecithin in Sesame is a treatment for dermatitis and dry skin. Other uses include the treatment of blurred vision, dizziness, headaches, and nasal mucosa dryness. In addition, Sesame features in a huge variety of folk remedies, with purposes ranging from burn treatment to increasing milk production in nursing mothers.

Unexpected exposure

Sesame is used in the production of perfumes, cosmetics, toiletries (especially UV-barrier creams), lubricants, insecticides and fungicides. The oil is sometimes burned for lighting. Sesame oil is a solvent for intramuscular injections and has been used in plasters, liniments, ointments, capsules, and emulsions, and in the formulation of medicinal suspensions and ophthalmic preparations. Liniment that contains Sesame oil has been used in the treatment of eczema and leg ulcers (2).

Sesame oil is often a "hidden allergen" in food. For example, pastries containing Sesame that are not sold may be "recycled" and thereby become a hidden allergen (3). Sesame meal is a feed for poultry and livestock.

Allergens

A wide range of IgE-binding proteins of Sesame seed has been identified: 78, 52, 45, 34, 32, 29, 25, 20, 9, and 7 kDa proteins (4). The proteins of white, brown and black Sesame extracts have been shown to have major quantitative differences (*e.g.*, white seeds have more protein than black seeds, 182 *vs*. 28 mg/g). The white extract contained 15 proteins of 12-79 kDa in size. Ten of the 15 proteins (12-57.5 kDa) bound to serum-specific IgE from Sesame seed-allergic individuals. The 12-13 kDa and 22-33 kDa proteins were thought to constitute the main allergens. Similar studies have reported that 2 proteins in this size range appear to be major allergens (5).

Similarly, in a study of the allergens of Sesame seed, serum of 12 Sesame-sensitised patients (7 with food allergy, 5 with food sensitisation) were utilised. Sesame protein extracts were prepared from black, white and brown Sesame seeds. Analysis showed similar protein patterns in the 3 extracts, and 19 protein bands were isolated. Two proteins, of 14 kDa and 25 kDa, were identified and shown to be the major allergens involved in Sesame IgE-dependent hypersensitivity, the 25 kDa band displaying several characteristics of a major allergen (6).

Insoluble 11S globulin and soluble 2S albumin, conventionally termed alpha-globulin and beta-globulin, are the 2 major storage proteins and constitute 60-70 and 15-25% of total Sesame proteins, respectively (7-9).

The following allergens have been characterised in Sesame seed:

Ses i 1, a 9 kDa protein, a 2S albumin (7,10-12).

Ses i 2, a 7 kDa protein, a 2S albumin (4,7,10).

Ses i 3, a 45 kDa, 7S vicilin-type globulin (4,10,13).

Ses i 4, a 17 kDa protein, an oleosin (10,14).

Ses i 5, a 15 kDa protein, an oleosin (10,14).

Ses i 6, a 11S globulin (7,10,15-16).

Ses i 7, a 11S globulin (7-8,10,15).

Ses i Profilin (17).

Ses i 1, a major protein and a 2S albumin, has been shown to be thermo-stable up to 90 °C and also highly resistant to digestion. After 2 hours of gastric digestion, the allergen remained completely intact, and only the small subunit was cloven during 2 hours of subsequent duodenal digestion, leaving a major IgE epitope region of this protein intact (12). Ses i 1 has been shown to be a potent allergen. Researchers have questioned whether the 9 kDa protein corresponds to a 2S albumin or a lipid transfer protein (18).

The 45 kDa protein, Ses i 3, a 7S vicilin-type globulin, a seed storage protein, binds to allergen-specific IgE in 75% of sera of Sesame-allergic patients. Ses i 2, a 7 kDa protein, is a 2S albumin, another seed storage protein of Sesame (4).

In some cases of severe allergy to Sesame seed, skin and serum tests do not produce any evidence of IgE reactivity. A study was done of the serum of 10 patients out of 32 who had displayed severe immediate symptoms and whose Sesame allergy was diagnosed by double-blind placebo-controlled food challenge or convincing clinical history, and in whom no specific skin

reactivity or serum IgE antibodies could be detected. In reducing conditions, 2 protein bands (15-17 kDa) could be separated from 2S albumin proteins and shown to be oleosins, which are present in oil body fractions. These proteins were recognised by IgE from all 10 patients' sera. The authors suggest that oleosins are major allergens of Sesame seed and may in particular be relevant to severe anaphylaxis. Falsely negative prick tests could be due to the lack of oleosins in presently available extracts, or to the epitopes being buried in the inner molecule. The oleosins were named Ses i 4 and Ses i 5 (14).

The 11S globulins, Ses i 6 and Ses i 7, have only 36% identity. In 24 patients with Sesame seed allergy, 13 showed strong IgE binding to recombinant Ses i 6, whereas 10 of the patients show clear binding to recombinant Ses i 7 (15).

Sesame seed has recently been shown to contain a lipid transfer protein. This protein appears to be most abundantly expressed in developing seeds but is also detected in flower tissues. The abundant LTPs in developing Sesame seed are involved in lipid transfer into the extracellular matrix (19). The allergenic potential of this LTP was not evaluated.

Potential cross-reactivity

Cross-reactivity between allergens in Sesame and allergens in other foods, including Hazel nut, Rye, Kiwi, Poppy seed, Black walnut, Cashew, Macadamia, Pistachio, and Peanuts, has been reported (2,20-21). One author attributed these cross-reactions to 2 broad causes: the first being multiple allergens, Sesame proteins or glycoproteins, present in Sesame seed and linked mainly to immediate hypersensitivity reactions mediated by IgE antibodies; and the second being lignin-like molecules in Sesame oil (sesamol, sesamin, and sesamolin, which are all reported to be unsaponifiable fractions of Sesame oil) (2).

Allergy to Kiwi, Poppy seeds, and/or Sesame seeds has been reported to often occur in patients with a simultaneous sensitisation to nuts and flour. These cross-reactions were verified by RAST inhibition studies reporting that the degree of cross-reactivity among Kiwi, Sesame seeds, Poppy seeds, Hazel nuts, and Rye was found to be very high in the patients studied. The existence of both cross-reacting and unique components was seen, but the authors reported that the cross-reacting and unique components could be different for different patients (20).

A study described 3 patients with severe immediate-type allergic reactions to Poppy seed, all of whom showed serologic positivity to Sesame seed. The authors suggested that this may have been due to cross-reactivity to similar allergens (22). The clinical relevance was not investigated further.

A known IgE-binding epitope of the Peanut allergen Ara h 1 has been shown to have an 80% homology with the corresponding area of the Ses i 3 allergen of Sesame seed. (But the amino acids concerned had been previously shown not to be critical for IgE binding in Ara h 1 of Peanut) (4). Furthermore, tree nut and Sesame allergy have been reported to occur more often in patients with Peanut allergy. Although this may be a coincidence, simply due to a predisposition to food allergy in these individuals, cross-reactivity has been demonstrated between Peanut and Sesame seed. A study described 3 patients, previously sensitised to but now tolerant of Peanut, who were diagnosed as having either tree nut or Sesame allergy. The study concluded that demonstration of tolerance to Peanut may give false assurance that patients no longer need to avoid tree nuts or Sesame; on the contrary, tree nut and Sesame allergy can exist or develop in patients despite the development of tolerance to Peanut (23).

The 19 kDa protein of Buckwheat has weak homology with the vicilin-like allergen of Cashew (Ana o 1), English walnut (Jug r 2) and 7 S globulin from *Sesamum indicum* (24).

The clinical relevance of Sesame profilin and its cross-reactivity have not been investigated (17).

Clinical Experience

IgE-mediated reactions

Sesame seed has become a significant and common inducer of food allergy symptoms in sensitised individuals; earlier reports of this allergy were quite infrequent (2,25-27). The prevalence of Sesame seed hypersensitivity is increasing due to the increasing popularity of vegetarian dishes, to Sesame's use in international fast-food and bakery products, and to the spread of Middle Eastern and Asian cuisines. Sesame seed is regarded as an "emerging" food allergen (9,28-33).

In an evaluation of the results of 4.5 million allergen-specific IgE antibody tests performed on Japanese individuals, Apple was found to have the highest number of positive tests, followed by Sesame seed (34). Similarly, Sesame was reported to be a major cause of IgE-mediated food allergy in Israel, and second only to Cow's milk as a cause of anaphylaxis. In 9,070 children, the food allergy prevalence was found to be 1.7%, with Sesame the third most common food causing sensitisation (0.18%), following Hen's egg (0.5%) and Cow's milk (0.3%), and exceeding Peanut sensitisation (0.04%). Sesame was second only to Cow's milk as a cause of anaphylaxis (35). In a French study, the prevalence of Sesame seed allergy was reported to be 2.14% in children and 5.81% in adults (36). A prevalence study of immediate hypersensitivity to foods among Australian children found that Sesame was in fourth place (0.42%), following Hen's egg (3.2%), Milk (2%), and Peanut (1.9%). Sensitivity to Sesame was more common than sensitivity to any single tree nut studied (32). In the report of a government research project in the United Kingdom in 1996, the estimated overall prevalence of severe allergic reactions to Sesame in the general population was 1 in 2,000 (0.05%) (37).

An early report describes 2 individuals who experienced severe allergic reactions with pruritus, generalised erythema, angioedema of the uvula, clinical shock and wheezing. The author suggested that Sesame seed should be considered an extremely potent allergen (38). Since then, numerous types of allergic reaction have been reported, including nausea, vomiting, diarrhoea, angioedema, angioedema of the tongue, burning of the mouth and lips, itching of the pharynx, symptoms of Oral Allergy Syndrome, wheezing, respiratory distress asthma, contact dermatitis and urticaria.

In a study of 14 children recruited from 3 allergy clinics in France, all of whom had a diagnosis of Sesame seed allergy based on a convincing clinical history and positive SPT or allergen-specific IgE, the median age for the onset of Sesame seed allergy was found to be 5 years (the range being from 5 months to 16 years). All patients reacted immediately after Sesame seed consumption, and they presented the following as a first manifestation: oedema (9 cases, 48%), and urticaria (5 cases, 27%), and 1 case of each of the following symptoms: vomiting, rhinitis, conjunctivitis, asthma and anaphylactic shock. One patient had recurrent anaphylactic shocks, and another an anaphylactic shock after a further Sesame seed exposure; these 2 patients were asthmatic. SPT with a commercial Sesame seed extract was less sensitive than with the native seed. The median of Sesame seed-specific IgE was 5.58 kU_A/l (range 0.35 to 100 kU_A/l). Three patients outgrew their food allergy. The authors reported that a spontaneous outgrowing of Sesame seed allergy can occur, but that predictive criteria could not be established (39).

In an Israeli study of 32 children with Sesame seed allergy, 3 subgroups were identified. Group I (n = 23) manifested IgE-mediated Sesame allergy. The mean age of the first allergic reaction was 11.7 months. The main clinical manifestation was urticaria/angioedema in 14 (60%), but anaphylaxis was the presenting symptom in 7 (30%) patients; all of these were younger than 1 year. Sixteen (70%) were found to be allergic to other foods, and other atopic diseases were identified in 18 (78%). Three patients "outgrew" their allergy within 1-2 years. In Group II (n = 2), Sesame allergy was ruled out based on the lack of positive SPT and a negative open oral challenge. Group III (n = 7) consisted of patients who were found to have skin reactivity for Sesame as part of a screening for other food allergies (40).

f10 Sesame seed

A study evaluating Ses i 6 and Ses i 7 described 24 patients with Sesame seed allergy. Clinical reactions involved the skin in 19 patients, and these reactions were mainly urticaria and angioedema; reactions involved the gastrointestinal tract in 11 patients, and the respiratory system in 6 patients. One patient had a decrease in blood pressure. Twelve patients had more than one organ system involved. Sesame seed-specific IgE levels ranged from 0.73 to greater than 100 kU_A/l (15).

Severe food-induced anaphylaxis has also been reported by many authors (6,10,41-43). Anaphylaxis to Sesame in a vegetable burger has been described (1,44). Sesame seeds were responsible for 3% of life-threatening allergic reactions to foods in France in 2002 (45). In Israel, Sesame was second only to Cow's milk as a cause of anaphylaxis (35,41). This may result from the high levels of exposure to Sesame in the Israeli diet, but although the use of Sesame in food is common in India, no published reports exist of Sesame allergy from this country (2). In a British study of Sesame allergy, 17% of respondents claimed to have suffered potentially life-threatening allergic symptoms, with 65% of severe reactions happening on first known exposure (46). A 6-year-old child who developed an anaphylactic reaction after eating bread and Sesame paste has been described (47). Significantly, not all Sesame-allergic individuals will have IgE antibodies directed at Sesame seed (9).

Sesame seeds are often present in gluten-free foods in therapeutic diets of coeliac patients; an instance of anaphylaxis in a coeliac patient following Sesame ingestion has been reported (48-49). Sesame seed can be regarded as a "hidden" allergen. Significantly, cases of severe allergy to Sesame seed may lack corroboration through SPT and IgE antibody determinations. The reasons for this are unknown. In a study of 32 patients who had displayed immediate symptoms such as anaphylactic shock, asthma, urticaria, and angioedema, Sesame allergy was diagnosed by double-blind placebo-controlled food challenge or a convincing clinical history. Ten patients had negative SPT and *in vitro* tests for Sesame. The authors were able to demonstrate that the allergens involved were oleosins (named Ses i 4 and Ses i 5), which appear to be major allergens of Sesame seeds and may be relevant to severe anaphylaxis (14).

Anaphylaxis has been described both to Sesame seed and Sesame oil (50-51). A study reports on 9 cases of IgE-dependent allergy to Sesame seed and/or Sesame seed oil. Commercial SPT were not very sensitive, whereas the sensitivity of SPT with a freshly prepared Sesame seed flour extract was greater. The diagnosis of this allergy was established by double-blind oral provocation tests, with doses of Sesame seed flour ranging from 100 mg to 10 g. Allergy to Sesame seed oil was also demonstrated in some of these cases (52). A previous report described generalised urticaria as a result of Sesame seed, but this could not be confirmed using SPT or allergen-specific IgE; instead, oral challenges confirmed it (53).

Immediate hypersensitivity reactions to Sesame in cosmetics have been reported (54).

An anaphylactic reaction to Cashew nut occurred in a non-atopic 60-year-old man 25 days after receiving a liver allograft from a 15-year-old atopic boy who died of anaphylaxis after Peanut ingestion. The liver recipient had no history of nut allergy. Post-transplantation skin prick test results were positive for Peanut, Cashew nut, and Sesame seed, and the donor had allergen-specific IgE antibodies to the same 3 allergens. This illustrates that transfer of IgE-mediated hypersensitivity can occur after liver transplantation and have serious consequences (55).

Occupational exposure to Sesame seed can occur though animal husbandry, bakery, mill and other work. Occupational asthma, rhinitis and urticaria due to Sesame seed contact have been reported (56-58). Systemic urticaria, facial erythema, dizziness and loss of consciousness were reported in a 36-year-old baker following exposure to Sesame. Commercial SPT and IgE antibody tests were negative, but SPT to crushed Sesame seeds in sodium chloride solution was detected (3).

Other reactions

Non-IgE-mediated reactions have been reported. A 45-year-old woman experienced facial erythema, flushing, generalised pruritus, and conjunctivitis after she had eaten crackers. Similar symptoms occurred several times after ingestion of Sesame oil in various preparations. Within minutes after ingestion of Sesame-dressed chicken, she had flushing, generalised itching, nausea, vomiting, and dizziness. Skin tests, including intra-cutaneous testing, were negative for common allergens. Skin testing using prick and scratch methods with native Sesame oil (cold-pressed and heat-extracted) and raw, peeled, crushed, and unpeeled Sesame seeds was negative. No IgE antibodies for Sesame seed or for common allergens was detected. In an oral challenge, 10 minutes after 2 bites of bread masking 10 g crushed Sesame seed and 10 g Sesame oil, the patient developed generalised flushing, itching, and conjunctival symptoms. Serum tryptase remained normal but urinary histamine increased (59).

If the extraction process for Sesame oil is not of a high standard, Sesame protein may be present in the oil, which can result in allergic reactions, including anaphylaxis, in sensitised individuals (60-62). Sesame seed oil may be used in cosmetics and pharmaceuticals, resulting in contact dermatitis, as described in 13 patients. The contact allergens sesamol, sesamin and sesamolin were identified in crude and purified (pharmaceutical) Sesame oil. Patch tests showed 8 of 13 patients to be positive to sesamol and 12 to sesamolin and sesamin (63). Cheilitis due to Sesame oil in a lipstick has been reported in a female patient. She reacted to sesamolin and sesamin, but not to sesamol. In this instance, sesamolin and sesamin were detected in the Sesame seed oil, but sesamol was not (52). Contact sensitivity to an ointment composed of 60% Sesame oil, used for the treatment of a burn on the forearm, has also been described. Contact dermatitis developed 10 days after application (64).

Salmonella outbreaks have been reported as a result of contaminated Sesame seed products, including halvah and tahini. An international outbreak of multiresistant *Salmonella typhimurium* that was correlated to the consumption of halvah resulted in an investigation of Sesame seed products. Out of 117 ready-to-eat food items containing Sesame, salmonella was isolated from 11 (9.4%). The products included Sesame paste (tahini) and Sesame seed sold for raw consumption in cereals (65). Similarly, in a report of 3 outbreaks of *Salmonella montevideo* infection in Australia and New Zealand, imported tahini was identified as the source of infection. Of a total of 66 cases of *S. montevideo* infections, 54 (82%) reportedly involved consumption of Sesame seed-based foods (66).

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f14 Soybean

Glycine max (Soja hispida)

Family:	*Fabaceae* (*Leguminosae*)
Common names:	Soybean, Soya Bean, Soy, Soya
Source material:	Dried beans

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Allergen Exposure

Geographical distribution

Soybean is the world's most important legume. Proteins of Soybeans are widely used in animal and human nutrition.

There are more than 200 varieties of Soybean. Soya is grown for edible green pods, half-ripe seeds, and dry seeds. Pods are rough and hairy and contain 3 or 4 seeds; these are smooth and vary in colour, being black, brown, green, yellow or white. The seeds have a higher protein content than do any other edible seeds.

During seed maturation, the membranous inner epidermis of the endocarp detaches from the pericarp, or pod wall, to cover the seed, influencing to varying degrees the luster of the seed surface (1). Different seed luster phenotypes have been described, including “shiny”, “intermediate”, “dull”, “bloom”, and “dense bloom” (2).

Soy protein consists of 136 phytochemicals (3). Soybean contains goitrogens, tannins, phytoestrogens, flatus-producing oligosaccharides, phytate, and saponins (4). Some of Soybean's phyto-chemicals have oestrogenic effects (5).

Environment

The bean can be used fresh, or can be processed into Soybean flour, flakes, grits, or Soy milk, or it can be pressed for oil. Soybeans are a primary foodstuff in Asia. Soybean oil is put to many uses. It is included in salad oil, margarine and industrial components, and in linoleum and glue in the plywood industry, where it is considered an occupational allergen. Soy sauce, or shoyu, is a fermented product of Soybean and Wheat.

Imitation cheeses may replace 30% of casein protein with Soya protein. Soya mince, a good source of protein, may be used as a replacement for meat or fish. Unlike other pulses, Soya beans have a healthy balance of amino acids and contain significant amounts of (mostly unsaturated) fat.

Unexpected exposure

Soya protein is found almost ubiquitously in processed foods, even in butter and margarine (6). In recent times, bread, including white bread, may contain Soy flour. In a Spanish study, the most frequent sources of hidden Soy allergens were boiled ham, sausages, cheese puffs, precooked dishes, desserts and gravy (7).

Reactions after unexpected food exposure

Soy proteins are frequently found in meat products, bread, and a wide range of industrially produced food products (8). Examples are Spanish sausage products (9), pizza (10), and candy containing Soy lecithin (11).

Soybean lecithin may be used in the baking industry, and baker's asthma as a result of exposure to Soybean lecithin has been described (13). Residual protein in Soy lecithin may also be involved in baker's asthma (12-13). Soybean lecithin allergy has been described in a child (11). Allergic reactions have also been reported to a Soybean protein isolate that comprised 50% of a dietary powder. Of these 20 patients,

85% were found to have IgE antibodies against Gly m 4, as well as to the major birch pollen allergen Bet v 1, suggesting an association of Birch pollen and Soy food allergy. Seventeen patients experienced facial, oropharyngeal, and/or systemic allergic symptoms within 20 minutes after ingesting the Soy product for the first time (14).

Soya bean oil is extracted from the Soybean and, if not purified, may still contain allergens, resulting in allergic reactions (15-16).

In a review of the role of hidden allergens in allergic reactions in Spanish patients, all the reactions caused by hidden allergens of legumes occurred in Soy-allergic patients, except for 1 lentil-allergic patient. Thirty-nine percent of the Soy-allergic patients had some reaction caused by Soy as a hidden allergen. The most frequent sources of hidden Soy allergens were boiled ham, sausages, cheese puffs, precooked dishes, desserts and gravy (7).

Several fatal reactions to Soy recorded in young asthmatics with known Peanut allergy but unrecognised sensitivity to Soy (17) reinforce the importance of proper labelling of food and the need for education of patients, school staff and healthcare personnel. Soybean is more frequently used as a substitute and constituent in many different foods, and therefore a higher frequency of adverse reactions to Soybean can be expected.

Interestingly, the transfer of Egg, Peanut, and Soybean sensitisation following bone marrow transplantation has been reported (18).

Allergens

Seed proteins in Soybean consist of 2 major fractions that account for 70% to 80% of the total protein: 11S albumins and 7S globulins. Approximately 6% of Soybean proteins are classified as inhibitors of trypsin and chymotrypsin, and approximately 0.5% are sugar-binding lectins. The 2 major classes of inhibitors are the Kunitz trypsin inhibitor, which inhibits trypsin, and the Bowman-Birk inhibitor, which inhibits both trypsin and chymotrypsin. These inhibitors and lectins can impair the nutritional quality and safety of Soy-based diets unless removed or inactivated (19-20).

There are at least 21 allergenic proteins in Soybean, ranging from 14 to78 kDa, that may result in IgE binding (21-24). A Kunitz trypsin inhibitor (as indicated above), glycinin, the alpha-subunit of beta-conglycinin, a P34/Gly m Bd 30K protein, a thiol protease, and a 50-kDa protein with homology to chlorophyll A-B binding protein have been identified as binding IgE of subjects with Soy allergy (20,25-27). In another study, sera of Soybean-allergic atopic dermatitis patients have been shown to recognise about 15 Soybean proteins, of which 3 were identified as major allergens: Gly m Bd 60K, Gly m Bd 30K, and Gly m Bd 28K (28).

In a study of 10 Soybean varieties, including those with a "dull" phenotype and those with a "shiny" phenotype, a 7 kDa band was present in all varieties except in those with a "shiny" phenotype. In *in vitro* tests, the varieties with a "shiny" phenotype contained fewer allergens than the other varieties studied. However, skin testing found no response differences among the Soybean varieties (2).

Soybean hulls also contain at least 3 unique main allergens; those with sizes of 8, 7.5, and 7 kDa have been identified (29). A large quantity of Soybean hydrophobic protein (HPS), a potentially hazardous allergen that causes asthma in Soybean dust-allergic individuals, is synthesised in the endocarp of the inner ovary wall and deposited on the seed surface during development. Its precise amount varies among Soybean cultivars and is greater on dull-seeded phenotypes (1).

During the process of harvesting, transport and storage, microbial and mold contamination can raise the temperature of Soybeans to 75 °C or higher. In a study using serum from 68 Soybean asthmatic subjects, it was demonstrated that the heat during storage and transport of Soybeans could generate 2 new allergen determinants or increase epitope exposure as a result of conformational changes. However, the clinical significance of this was not assessed (30).

f14 Soybean

Hydrolysis or fermentation of Soybean in the manufacture of fermented Soybean products, including miso, tempeh, tofu, and mold-hydrolyzed Soy sauce, has been shown to reduce allergenicity. Depending on the extent of hydrolysis or fermentation, a proportion of Soybean allergens may remain in the processed vegetable proteins (31). In a study of sera of patients with delayed hypersensitivity to fermented Soybean, 6 allergens, including 3 of 38, 28, and 26 kDa, were demonstrated (32). Properly manufactured Soy sauce is reported to have no residual allergic activity (33).

The following allergens have been characterised:

Gly m 1, a 7-8 kDa protein, a HPS, Soybean hydrophobic protein, a major allergen (29-30,34-40).

Gly m 2, an 8 kDa protein, a major allergen (29-30,34,36,41).

Gly m 3, a 12-15 kDa protein, a profilin, a major allergen (25,34,42-44).

Gly m 4, a Bet v 1 homologue (Group 1 Fagales-related protein), a major allergen, previously known as Gly m SAM22 (14,25,34,45).

Gly m 2S Albumin, a 2S Albumin (46-48).

Gly m 39kD, a 39 kDa protein, a major allergen (47,49).

Gly m Bd28K, a 28 kDa protein, a 7S Vicilin-like globulin, a major allergen (50-56).

Gly m Bd30K, a 30-34 kDa protein, a thiol protease of the papain superfamily, a major allergen, also known as P34. (21,26,57-66).

Gly m Lectin, lectin, SBA, an agglutinin, a major allergen (67).

Gly m Bd 60K, a 63-67 kDa protein, a major allergen (28,43).

Gly m TI, a 20 kDa protein, a trypsin inhibitor, a major allergen (27,47,68-70).

Gly m Oleosin, an oleosin (71).

Gly m IFR, an isoflavone reductase (72).

Gly m Glycinin G1, a glycinin, a major allergen (73).

Gly m Glycinin G2, a glycinin, a major allergen (73).

Gly m Glycinin G4, a glycinin, a major allergen (73).

A class 1 chitinase has been isolated from Soybean seed coat (74). Its allergenicity was not assessed.

Different Soybean allergens are involved in inhalation and food allergy. Furthermore, the allergens involved in occupational asthma caused by Soybean flour are predominantly high-molecular-weight proteins that are present in both the hull and flour of Soybeans; they are different from the allergens that cause asthma outbreaks from Soybean dust, allergens that are mainly low-molecular-weight proteins concentrated in the hull, *e.g.*, Gly m 1 (36,75). Airborne Soybean hull proteins are known causes of asthma epidemics around harbours and Soy processing plants, whereas Soy flour dust proteins may cause occupational allergy in food and feed industries (76). Individuals in rural areas where Soybean is grown and harvested may also be exposed to Soybean dust by inhalation (77).

Nonetheless, heterogenous sensitisation to Soybean allergens appears to occur. An evaluation was done of the main Soybean hull allergens using the sera of 18 asthmatic patients affected by the Soybean dust asthma epidemic in Barcelona. allergen-specific IgE in 15 of the 18 (83.3%) sera was demonstrated. In 11 sera, allergens of 8, 7.5 and 7 kDa were detected, which are the molecular weights described for Gly m 2, Gly m 1A and Gly m 1B, respectively. In 3 sera, an allergen with an estimated size of 8.2-8.3 kDa and 4 others of 25-36 kDa were detected. The study confirmed that Soybean hulls contain major allergens and additional higher-molecular-weight allergens, which selectively bind specific IgE of the sera that do not react with the 3 low-molecular-weight components; there is a dichotomous and non-overlapping pattern (29). The same authors demonstrated that in occupational asthma in Soybean-exposed bakers, IgE-binding occurs mainly to high-molecular-weight allergens: none of the patients showed IgE-reactivity against the low-molecular-weight protein Gly m 1, and only

1 patient showed IgE-reactivity to the Soybean hull allergen Gly m 2 (36).

Similarly, in a recent study to determine the clinical characteristics of Soy allergy in Europe, the pattern of IgE reactivity against proteins with molecular weights of between approximately 10 and 70 kDa was highly individual among the patients and did not correlate with the severity of symptoms (78).

In Soybean food allergy, the most important allergen is a protein termed P34 (Gly m Bd30K), which is abundant in the seeds and other parts of the plant (2).

The low-molecular-weight Soybean allergens Gly m 1 and Gly m 2 are found in Soybean dust. Gly m 1, although abundant in Soybean dust, occurs in all parts of the Soybean plant at all stages of growth; but the telae (hulls) and pods are by far the richest source (79). These 2 allergens were shown to be responsible for epidemic asthma outbreaks resulting from Soy dust (36). Gly m 1 occurs in the form of isoallergens named Gly m IA (protein S2) and Gly m IB (protein S1), which were recognised by IgE antibodies from 95% of patients who suffered asthma attacks during these asthma outbreaks of 1987 and 1988 in Cartagena, Spain (39).

Gly m 3 is a profilin, a panallergen. In a study of serum from 13 Soybean-sensitised subjects, IgE antibodies to recombinant Gly m 3 was detected in 9 (69%) (43).

A study was done of 22 patients allergic to Birch pollen who also had Soy allergy, and among whom 10 experienced symptoms localised to the oral cavity, while 6 had a more severe reaction following a Soy challenge. Gly m 4-specific IgE was found in 96% (21/22) of the patients. All patients had Bet v 1-specific IgE antibodies, and 23% (5/22) had positive Bet v 2 results. Gly m 4 is a Bet v 1 homologue. In IgE immunoblotting, 25% (6/22) of the patients recognised Gly m 3 (profilin), and 64% (14/22) recognised other Soy proteins. IgE binding to Soy was at least 80% inhibited by Birch pollen and 60% inhibited by rGly m 4 in 9 of 11 sera tested. Seventy-one percent (67/94) of highly Bet v 1-sensitised patients with Birch pollen allergy were sensitised to Gly m 4, and 9 (9.6%) of those patients reported Soy allergy, confirming that Soybean is a Birch pollen-related allergenic food. The authors concluded that Gly m 4 is the major Soy allergen for patients allergic to Birch pollen who also have Soy allergy (25).

Similarly, in a study investigating IgE-mediated reactions to a Soy-containing diet food product in patients allergic to Birch pollen, significant IgE binding was demonstrated to the Soy isolate rSAM22 (rGly m 4) in 17 of 20 patients. Other allergenic proteins of 17 kDa (15/20), 22 kDa (1/20), and 35 to 38 kDa (2/20) were also isolated from the Soy isolate (14).

Targeting Gly m 4 in diagnostic assessment may facilitate an improvement of diagnostic sensitivity. This substance was used as a allergen-specific reagent in a study of 22 individuals with pollen-related allergy to Soybean. While only 10 out of the 22 (45%) showed positive in a Soybean extract-based test, all but 1 (96%) showed IgE binding to rGly m 4 coupled to streptavidin-coupled ImmunoCAP tests (25,80).

Soybean seeds contain a pair of 2S albumin storage proteins, AL1 and AL3. These 2S albumins were shown to be stable to heat and chemical treatments (46). Soybean 2S albumins have been reported to be minor allergens in a British patient population assessed (48).

Gly m Bd 28 K is a major Soybean glycoprotein allergen. It was originally identified as a 28 kDa polypeptide in Soybean seed flour. In a study of sera from Soy-sensitised adults, all sera contained IgE antibodies that recognised the C-terminal region of this allergen. Gly m Bd 28 K contains 2 cupin domains (56).

Gly m Bd 30K is also known as a Soybean oil-body-associated glycoprotein that is homologous to Der p (or Der f) 1, a major allergen of House dust mite, classified under the Papain superfamily (28). Gly m Bd 30K (P34) is an outlying member of the Papain superfamily of cysteine proteases. It is expressed in developing Soybean seeds and may be involved in the defence against Pseudomonas infection. P34 was reported to be the major allergen of Soybean seed and

is present in processed food products that contain Soybean protein. In an evaluation of Soybean accessions, all contained similar levels of P34. Wild relatives of Soybean were also shown to contain P34. Extracts from all were shown to bind IgE antibodies from patients with clinically significant Soybean allergy (66).

Sensitisation to Gly m TI, a trypsin inhibitor, was evaluated in 14 bakers suffering from workplace-related respiratory symptoms and sensitised to Soybean. Gly m TI was found to be a major inhalant Soybean allergen, recognised by IgE antibodies in sera of 86% of the group. The Soybean lipoxidase was also found to be a major allergen in this group (69).

Soybean trypsin inhibitor was also evaluated in sera of 5 patients with atopic dermatitis and a positive food challenge to Soybean, and found to bind to IgE antibodies in only 20% of these patients (27).

Soybean oleosins are a family of small proteins involved in the formation of Soybean oil bodies; they are similar to Peanut oleosins. Oil bodies are small organelles that hold the reserve oils of seeds and consist mainly of triglycerides, phospholipids, and a few polypeptides (21). In a study of IgE binding with Peanut oleosin, the phenomenon was demonstrated in 3 of 14 sera of patients who had suffered an allergic reaction to Peanut; the main reacting bands had a molecular size estimated at approximately 34 kDa, approximately 50 kDa and approximately 68 kDa, and the size was thought to correspond to oleosin oligomers. The same occurred with crude Soybean oil fractions, with 2 bands of 16.5 and 24 kDa corresponding to monomers, and 2 bands of 50 kDa and 76 kDa corresponding to dimers and trimers, respectively (71).

Soybean glycinin and beta-conglycinin represent up to a third of protein in Soybean. Glycinin and beta-conglycinin have been characterised as major Soybean allergens involved in food hypersensitivity (81). Soy glycinin is resistant to processing (82) and stable to degradation by simulated gastric fluid (83).

The 70 kDa subunit of beta-conglycinin was shown to be recognised by 25% of Soybean-sensitive patients with atopic dermatitis. Data suggests that at least 1 epitope is located within a non-glycosylated fragment consisting of about 50 amino acid residues. The beta-conglycinin alpha subunit has been demonstrated to be able to induce anaphylaxis through an IgE mediated mechanism (73).

The storage protein glycinin accounts for about 35% of the protein content of the Soybean. It consists of 6 subunits, each of them consisting of 2 peptide chains (1 acidic and 1 basic) held together by disulfide bonds (84). The acidic peptides were found to be responsible for much but not all of the IgE binding activity of glycinin.

Potential cross-reactivity

Earlier studies of Soybean demonstrated several antigenic components with considerable cross-reactivity with other legume family members (85). While the clinical usefulness of eliminating legumes from the diet of allergic patients is disputed, several reports confirm cross-reactivity. A patient who suffered adverse reactions when eating Peas, Lentils, Peanuts, Kidney, Lima and Navy beans experienced the most severe episodes following ingestion of Soybean products (86). A specific IgE antibody response to the Kunitz Soybean trypsin inhibitor polypeptide was demonstrated.

Patients experiencing IgE-mediated symptoms after ingestion of Pea, Bean, Lentil, Peanut and Soybean have been reported, but no single patient was allergic to all (87). Similarly, in a study of Soybean sensitive-children, a high correlation of concomitant sensitisation to Pea (38/50) and Peanut (41/50) was reported (88). However, though studies have reported *in vitro* cross-reactivity between Peanut and other legumes, *e.g.* Pea, Kidney beans, and Lentil, this was not supported by clinical challenge (89). Similarly, in 22 patients who experienced adverse reactions to Lentils, 14 also had experienced immediate allergic reactions to Chick pea, and 10 to Peanut; none had experienced adverse effects to Soy or Soy-derived

products. Yet all were shown to have allergy-specific IgE to all 4 legumes (90).

It has been suggested that individuals allergic to both Peanut and Soybean have IgE antibodies binding preferentially to the larger proteins, while the antibodies of those reacting only to Soybean bind strongly to proteins in the lower-molecular-weight range (22,24). Studies on 2 patients both allergic to Peanut and Soy showed extensive cross-reactivity between the 2 legume seeds (91). Several major Peanut allergens have been shown to share epitopes with Soy storage proteins. (For further information, see Peanut f13.)

An 8 kDa allergen prepared from Soybean hull shows 71% homology with a storage protein from Cow pea and 64% homology with a protein from Pea. A 17 kDa Soy allergen has also been found to cross-react with a Pea allergen (92).

It is therefore apparent that Soy-allergic individuals may be sensitised to Soybean and a number of other legumes, but may be clinically unaffected by any or all of these legumes unless a particular cross-reactive Soybean panallergen is involved.

Soybean contains a number of cross-reactive panallergens that have been characterised and may explain the patterns of co-sensitisation reported previously. With recent advances in diagnostics, the precise diagnosis of the specific Soy allergens involved may allow the deduction of potential sensitisation to other legume family members that contain the homologous allergen.

For example, Gly m 3, a profilin, is a panallergen. In a study of serum from 13 Soybean-sensitised subjects, IgE antibodies to recombinant Gly m 3 was detected in 9 (69%). The rGly m 3 cross-reacted with Bet v 2, the Birch tree pollen profilin. IgE binding to Bet v 2 could be inhibited by rGly m 3 (43).

A study was done of 22 Birch pollen-allergic patients also allergic to Soy. During food challenge, 10 patients experienced oral allergy syndrome, and 6 patients had a more severe reaction. Gly m 4-specific IgE was found in 96% (21/22) of the patients. All patients had Bet v 1-specific IgE antibodies, and 23% (5/22) had positive Bet v 2 results. In IgE immunoblotting, 25% (6/22) of the patients recognised Soy profilin (Gly m 3), and 64% (14/22) recognised other Soy proteins. IgE binding to Soy was at least 80% inhibited by Birch pollen and 60% inhibited by rGly m 4 in 9 of 11 sera tested. Seventy-one percent (67/94) of highly Bet v 1-sensitised patients with Birch pollen allergy were sensitised to Gly m 4, and 9 (9.6%) of those patients reported Soy allergy. The authors concluded that these results confirmed that Soybean is another Birch pollen-related allergenic food and that Gly m 4 was the major allergen for patients allergic to Birch pollen and also Soy (25). In a further study, in which the authors assessed 10 Mung bean-allergic subjects with concomitant respiratory allergy to Birch tree pollen for sensitisation to Vig r 1, a Bet v 1-homolous allergen, it was reported that 90% were sensitised to Gly m 4 (93). Further evidence for Bet v 1-homologue cross-reactivity was demonstrated between Gly m 4, Ara h 8 from Peanut, and Pru av 1 from Cherry (45).

In a report on 3 patients who experienced anaphylaxis to a Soy drink, cross-reactivity of Soy protein with Birch pollen allergens was identified as the cause of their severe reactions. The authors suggested that patients with Birch pollen allergy should avoid the intake of Soy protein (94).

Soybean glycinin G1 acidic chain has been reported to share IgE epitopes with Ara h 3 from Peanut, with a sequence similarity of 62% between the Soy glycinin and Ara h 3 from Peanut (95).

Soybean-specific IgE has also been reported to be cross-reactive with Potato. SPT evaluation for Soybean and fresh Potato was performed in 177 children of less than 4 years of age who were suspected of having food allergy. Further, sera from 17 children with suspected Potato allergy and 12 children with suspected Soy allergy were evaluated for IgE antibodies to natural Sola t 2-4 and Kunitz-type Soybean trypsin inhibitor (KSTI). Skin reactivity for Soybean was demonstrated in 10/177 (5%) and for Potato in 14 (7%). Of those with positive SPT for Potato, 70% had IgE antibodies to

KSTI and 75% to Soybean. However, of those suspected of having allergy to Soybean, 9 (75%) had IgE antibodies to Sola t 2-4. Cross-inhibition was demonstrated for Sola t 2-4 and KSTI. The study concluded that children with suspected food allergy frequently have SPT reactivity for Soybean and Potato; and it may be due to cross-reactive IgE antibodies against structurally altered Potato allergens, and *vice versa*: and that this should be considered when examining children suspected of having Soybean or Potato allergy (96).

Clinical Experience

IgE-mediated reactions

Soybean may commonly induce symptoms of food allergy in sensitised individuals. Dust from Soybean storage or transport has been reported to result in exacerbation of asthma, and dust from Soybean flour may precipitate asthma in bakers (36,77).

There are 2 main types of Soy food-allergenic reactions. IgE-mediated reactions may result in respiratory, cutaneous, and gastrointestinal symptoms, and anaphylaxis. Delayed non-IgE-mediated reactions, including Soy-induced enterocolitis, may be experienced (21,97-98).

Soybean is often cited as one of the foods to which children experience IgE-mediated reactions (99-100). The prevalence of Soy bean sensitisation in a group of 317 Italian children (median age 5 months) with symptoms suggesting food allergy was 22% (101.) In another study, 37/78 (47%) of Australian children with Cow's milk allergy were reported to react to Soy at a follow-up 5 years later (102).

In an analysis of 580 French patients with reactions to food, of whom 60 presented with severe, near-fatal reactions, Soybean was implicated in 30%, the fifth most common cause after Wheat (39%), Peanut (37%), Crab (34%), and Celery (30%) (103).

Recent studies have also focussed on threshold levels that precipitate symptoms. In a recent study to determine the clinical characteristics of Soy allergy in Europe, Soy-allergic patients underwent a titrated, double-blind, placebo-controlled food challenge. All patients but 1 responded primarily with subjective symptoms to the challenge, followed by objective symptoms in 11 subjects, with symptoms ranging from rhinitis up to a decrease in blood pressure. Cumulative threshold doses for allergic reactions ranged from 10 mg to 50 g for subjective symptoms and from 454 mg to 50 g for objective symptoms. The study concluded that in a statistical model, 1% of patients with Soy allergy would react subjectively with 0.21 mg of Soy protein, and objectively with 37.2 mg of Soy protein, and that both the clinical and immunologic bases of Soy allergy in Europe are highly complex. None of the patients with Soy allergy reacted to the starting dose of 2 mg of Soy (1 mg of Soy protein) (78). An earlier statistical model projected that 0.3 g of Soy flour will elicit an allergic response in 1 out of every 100 Soy-sensitive people (104).

A number of studies concluded that Soybean, among other foods, may be a common food allergen in atopic dermatitis in children (105). In 165 American patients aged 4 months to 22 years and having atopic dermatitis, 7 foods (Milk, Egg, Peanut, Soy, Wheat, Cod/Catfish, Cashew) accounted for 89% of the positive challenges (106). In an American study, 28% of 53 Soy-sensitive children with atopic dermatitis exhibited an allergic response after ingesting less than 0.5 g of Soy flour. This corresponds to approximately 41 mg of Soy protein (107).

There is evidence that Soy allergens may pass to infants through breast milk, resulting in sensitisation. In a study of a selected population of 59 predominantly breast-fed young Australian infants (mean age 26.5 weeks) who had moderate to severe generalised atopic dermatitis, 53 infants (90%) had demonstrable skin reactivity to 1 or more of the 5 common food allergens (Egg white, Cow's milk, Peanut, Wheat or Soy), and 80% were positive to Egg white (108).

The fact that Soy reactions are not always obviously immediate may confuse the interpretation of challenge tests. In a re-challenge of 18 Australian infants who had stabilised after feeding with a non-allergenic diet, 12 were found to react to formulas that

previously had not been tolerated. The infants (median age 7 1/2 months) were given Neocate formula for 2 months and then underwent a 7-day double-blind placebo-controlled challenge with the formula previously best tolerated. In 12 of the 18 infants, irritability, vomiting, diarrhoea, and/or eczema flares developed during the challenge. However, only 2 showed immediate symptoms. In the remaining 10, symptoms evolved after 4 to 7 days of challenge. Adverse reactions occurred to a Soy formula in 6 patients, to Whey hydrolysate in 2, and to Casein hydrolysate in 4 (109).

Although Soybean is considered a "classical food allergen" (89), it has long been regarded as a safe food substitute for children showing adverse reactions to Cow's milk. However, about a fourth of Cow's milk-sensitive patients may become allergic to Soy protein (110-111). It was found that Soy formula did not lower the cumulative incidence of atopic disease, as compared with Cow's milk (112). Breast-feeding or less allergenic formulas should be preferred, but socioeconomic conditions and other risk factors should be considered (113-114).

Soybean ingestion may result in anaphylaxis, inducing respiratory, cutaneous, cardiovascular, and gastro-intestinal symptoms, and even death (115-116). Soybean food-dependant exercise-induced anaphylaxis has been reported (117). Authors have cautioned that Soy protein may be an underestimated cause of food anaphylaxis. In a study of anaphylactic reactions to Soy, the majority of patients had a symptom-free period of 30-90 minutes between the early mild symptoms and the later severe and rapidly worsening asthma (17).

Anaphylaxis to fermented Soybean has also been reported. Researchers have hypothesised that the mechanism of late-onset anaphylaxis to fermented Soybeans is delayed absorption or release into the bowel rather than an immunologic phenomenon. In a Japanese study of 2 patients with demonstrable skin reactivity to fermented Soybean and IgE antibodies to Soybean, challenge with 50 g of fermented Soybeans caused generalised urticaria and dyspnoea 13 hours later in 1 patient. Plasma histamine and tryptase levels were transiently elevated during the anaphylactic event (118).

Anaphylaxis had also been reported following ingestion of Soy drink in 3 German individuals. The authors concluded that the cause of the severe Soy reactions was cross-reactivity of Soy protein with Birch pollen allergens. The authors suggested that patients with Birch pollen allergy should avoid the intake of Soy protein (94). Other authors have also concluded that Birch pollen and Soybean hypersensitivity may occur as a result of cross-reactivity; they hold that Gly m 4, a Bet v 1-homologue, is the allergen causing Soy-related symptoms. Symptoms caused by different Soy-based commercial products ranged from OAS to anaphylaxis (25).

In studies in Japan, IgE antibodies to Soybean were measured by the Pharmacia CAP System (119-121). Sensitivity and specificity were 100% and 87%, respectively (119).

Soy dust asthma and epidemic asthma

The allergens involved in causing asthma outbreaks are mainly low-molecular-weight proteins concentrated in the hull, whereas the allergens involved in occupational asthma caused by Soybean flour are predominantly high-molecular-weight proteins that are present both in the hull and flour (36).

Epidemic asthma in areas around harbours where Soybeans are unloaded from ships has been reported from Barcelona (122), Cartagena (123), Tarragona (124), Valencia (125), A Coruña (125), Naples (126), New Orleans (127), and New Zealand (128). A large number of fatal cases, probably resulting from anaphylaxis, were recorded. The major allergens involved were found in the hull of the bean (although they are also present in other parts of the bean) (37,41,79,123-124,129). All the asthmatic epidemic patients from Barcelona were shown to have IgE antibodies for Soybean (129), and the prevalence of Soybean sensitivity in the Cartagena incident was reported to be 89% (130). Soybean hull antigens were also shown to be involved in hypersensitivity pneumonitis (131), and

irritant effects of Soy dust may contribute to the development of respiratory problems in Soy mill workers (132).

As this suggests, Soybean hull dust may also occur at work (for example, in storage areas) and may result in occupational asthma without flour-related bronchoconstriction (133).

Soy dust allergens have been shown to be sporadically present in the air in a region where Soybeans are extensively grown, and were most prevalent during the harvest period. The highest level recorded was 73 ng/m^3 (35).

Rhinitis, conjunctivitis and bronchospasm following the inhalation of Soybean dust from a "bean bag" toy have been reported (134).

Baker's asthma

Occupational asthma in bakers, millers and workers in food processing plants may be caused by Soy flour. The reported prevalence of Soy sensitisation in bakers with workplace-related respiratory symptoms ranges from 19% (135) to 25% (36,136).

The Soybean allergens causing occupational asthma in exposed bakers were investigated and compared with those involved in epidemic asthma. The subjects were 4 bakers and confectioners with work-related respiratory symptoms who were exposed to Soybean flour. Sensitisation to Soybean flour was demonstrated by allergen-specific IgE evaluation and was confirmed by positive bronchial challenge tests, which elicited immediate or dual asthmatic responses. IgE-binding occurred mainly to high-molecular-weight allergens, and no one showed IgE-reactivity against the predominant hull allergen Gly m 1. Only 1 patient showed IgE-reactivity to the Soybean hull allergen Gly m 2. The study concluded that these bakery workers had developed IgE-mediated occupational asthma to Soybean flour and that the allergens involved in occupational asthma caused by Soybean flour are predominantly high-MW proteins that are present both in the hull and flour; and that these allergens are different from the allergens causing asthma outbreaks, which are mainly low-MW proteins concentrated in the hull (36).

Animal food processing plant workers may also come into contact with Soybean flour, resulting in sensitisation. In 35 men working in an animal food processing plant, the most frequent sensitisation was to fish flour (82.9%), followed by carotene (77.1%), Corn (65.7%), Four-leaf clover (62.9%), Sunflower (54.3%), Chicken meat (31.4%), Soy (28.6%), and Yeast (22.7%). (137) There may be a long delay between the initial contact and subsequent sensitisation, as described in a 43-year-old woman who developed asthma 6 years after beginning work in a food-processing plant in which Soybean flour was used as a protein extender. Symptoms of sneezing, coughing, and wheezing would begin within minutes of exposure to Soybean flour and resolve 2 hours after exposure ceased (92).

Other reactions

Food protein-induced enterocolitis (FPIES) in infants as a result of Soy ingestion has been reported by a number of authors. Cow's milk is also a prominent cause, although other foods may also be implicated (138-140). FPIES is a severe cell-mediated gastrointestinal food hypersensitivity and is characterised by symptoms occurring several hours after ingestion of a food or foods. Symptoms typically begin in the first month of life along with failure to thrive and may progress to acidemia and shock. Typical symptoms of FPIES are delayed (median 2 hours) and include vomiting, diarrhoea, lethargy and dehydration (141). Resolution of symptoms occurs after removal of the causal protein from the diet, but symptoms recur with a characteristic pattern on re-exposure. Approximately 2 hours after reintroduction of the protein, vomiting ensues, followed by an elevation of the peripheral blood polymorphonuclear leukocyte count and diarrhoea. Lethargy and hypotension may also occur. IgE antibodies to the causal food is generally not present (140,142). An early study on a small group of children with "Soy intolerance" (suspected enterocholitis) was not conclusive in terms of the role of antibodies, although

IgE antibodies to several fractions were found. The source and quality of the Soy protein used in challenge tests was not declared (143). It has been proposed that the presence of IgE antibodies to the allergen involved may be helpful in predicting long-lasting sensitivity (140).

Eosinophilic esophagitis is a disorder identified in patients with symptoms suggestive of gastroesophageal reflux disease but unresponsive to conventional reflux therapies. In a study of 146 patients diagnosed as having eosinophilic esophagitis, as evaluated by skin prick and atopy patch testing, Egg, Cow's Milk, and Soy sensitivity were identified most frequently by skin prick testing, whereas Corn, Soy, and Wheat sensitivity were identified most frequently with atopy patch testing. In more than 75% of patients with eosinophilic esophagitis, both outward symptoms and esophageal inflammation were significantly improved with dietary elimination of foods (144).

Symptoms of allergy to Soy may be atypical. A 39-year-old woman was reported who complained of respiratory symptoms such as dry cough and mild dyspnoea occurring after the ingestion of food containing Soya (145). An association between recurrent serous otitis media and food allergy has been described in 81 of 104 patients. An elimination diet resulted in a significant amelioration of the disease in 86% of the patients, and a challenge diet provoked recurrence of symptoms in 94%. The highest frequency of sensitivity was seen with Milk, Wheat, Egg, Peanut, Soy and Corn (146).

After measuring Soy-specific IgA and IgG antibodies in children with Soy intolerance and with coeliac disease, investigators concluded that the observed increase of IgA antibodies correlated to mucosal injury, while the increase of IgG antibodies was related to the increase of antigen entry (147).

Mold contamination of Soybean may occur with storage and transport and theoretically may result in sensitisation, depending on the organism involved (30). Aflatoxins have been reported in Soybeans (148).

Various Wheat and Soy protein sources, including the Soy protein isolates used to make infant formulas, have been said to be causally involved in to juvenile or insulin-dependent diabetes mellitus (IDDM) (149).

Unexpected allergens from other organisms may someday occur in Soy. Progress in biotechnology, which allows the introduction of alien genes for the purpose of improving properties of crops, has opened the way for new potential allergy risks. The fact that alien allergens can be and have been introduced into Soybean (150) has stimulated the discussion of potential changes of allergenicity in transgenic food (151-152). But it is obvious that the analysis of potential risks for sensitisation is difficult until a human population has been exposed.

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f124 Spelt wheat

Triticum spelta

Family:	*Poaceae* (*Gramineae*)
Common names:	Spelt, Spelt wheat
Source material:	Untreated planting seeds
Synonym:	*Triticum aestivum subsp. spelta*

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Allergen Exposure

Geographical distribution

Spelt (*Triticum spelta*) is a hexaploid species of Wheat. Spelt was an important staple in parts of Europe from the Bronze Age to medieval times; it now survives as a relict crop in Central Europe and has found a new market as a health food. Spelt has a complex history. It is sometimes considered a subspecies of the closely related species Common wheat (*T. aestivum*), in which case its botanical name is considered to be *Triticum aestivum subsp. spelta* (1). From genetic evidence, it appears to have originated as a hybrid of domesticated tetraploid Wheat such as Emmer wheat and the wild goat-grass *Aegilops tauschii* (2).

"Wheats", as defined by US and Codex standards, can have either 28 chromosomes (*e.g.*, for Durum wheat) or 42 chromosomes (*e.g.*, for Common wheat or Club wheat). Spelt has the same number of chromosomes and the same 3 "genome blocks" as Common wheat and Club wheat (3). Scientific evidence shows that there is a high percentage of homology between the proteins of Spelt and those of Common wheat (4).

Environment

Spelt may be ground into flour for Wheat-like products, *e.g.*, Spelt pasta. Spelt products are available mostly from speciality stores, although Spelt flour is becoming more easily available, being recently sold in UK supermarkets.

In Germany, the unripe Spelt grains are dried and eaten as Grünkern, which literally means "green grain".

The Dutch distil Spelt to make a curiosity gin, jenever. Beer brewed from Spelt is sometimes seen in Bavaria (5).

Spelt matza is baked in Israel for Passover and is available in some US grocery stores (1).

Unexpected exposure

Spelt has recently been marketed as safe for Wheat-allergic or Wheat-intolerant individuals. This claim is anecdotal and not scientifically supported.

Wheat-allergic patients can react as readily to Spelt as they do to Common wheat. Furthermore, Spelt is not suitable for people with coeliac disease.

Allergens

The following allergen has been characterised:

Tri s LTP, a 9 kDa lipid transfer protein (6).

Potential cross-reactivity

As Spelt and Common wheat are from the same genus, *Triticum*, a high percentage of homology between the proteins of Spelt and those of Common wheat is expected. This is supported by laboratory data showing high specificity of real-time Wheat PCR in detecting Spelt and other *Triticum* species (7). Furthermore, the National Center for Biotechnology Information Entrez data base contains 97 sequences for Spelt proteins, and these sequences are > 95% identical to "Common wheat" protein sequences. In addition, the single sequence for a Spelt protein that is known to be a Wheat allergen, alpha-gliadin (accession ABB17533), is 99% identical to a homologous Wheat protein (accession CAB76957). Therefore, cross-reactivity may be similar to that reported for Wheat. See Wheat f4.

As Spelt contains a lipid transfer protein, cross-reactivity with other plants containing lipid transfer proteins is possible. This is demonstrated by a report of occupational sensitisation to Spelt that was associated with symptoms on ingestion of several lipid transfer protein-containing foods. In particular, the individual was unable to tolerate the cross-reactive foods Peach and Apricot (6).

Clinical Experience

IgE-mediated reactions

Unexpectedly, allergic reactions to Spelt have not been commonly reported. This may be a result of Spelt products not being commonly available. Reported adverse reactions are expected to increase as Spelt and Spelt products become increasingly more accessible. Adverse reactions may be similar to those reported to Wheat. See Wheat f4.

A case report describes an individual with a demonstrated allergy to Common Wheat who had several similar anaphylactic reactions after consuming Spelt (8).

Occupational dermatitis was reported in a 25-year-old woman, following exposure to large amounts of Spelt in her occupational setting. This was followed by generalised reactions to other foods. Within few months after avoiding Spelt and changing her occupation, her food symptoms and sensitisation disappeared, and the patient could reintroduce into the diet all foods that she previously did not tolerate, except for Peach and Apricot. A lipid transfer protein in Spelt was identified as the dominant allergen and responsible for the cross-reactivity (6,9).

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f227 Sugar-beet seed

Beta vulgaris

Family:	*Amaranthaceae* (*Chenopodiaceae*)
Common names:	Sugar-beet seed, Sugar beet seed
Source material:	Dried seeds
See also:	Sugar-beet w210

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Allergen Exposure

Geographical distribution

Beta vulgaris produces sugar from its large, white, conical tap roots. Large-scale cultivation in Europe began during the Napoleonic wars when the British blockade stopped imports of sugar cane from the West Indies. The Sugar-beet is native to Europe and the Middle East but is now cultivated worldwide as a commercial sugar crop in temperate climates. About a third of all sugar production in the world is derived from this plant, but this sugar is considered inferior to cane sugar because it does not crystallise as well and is absorbed more quickly by the body

Sugar beet is an annual or biennial plant growing to 1.5 m. The leaves are oval in shape and dark green or reddish in colour, frequently forming a rosette from the underground stem. The flowers are small and green or red. The Sugar-beet seed is tiny – about half the size of a grain of rice – and rough and bumpy, growing in clusters inside the dry fruit.

Environment

Beets and their relatives are grown throughout the world for human and stock food. The seeds, apart from some isolated culinary uses (as in India and Pakistan), serve as an animal feed.

Allergens

No allergens from the seed of this plant have yet been characterised, but a number of proteins have been isolated from the leaves.

A protein with homology to the chitin-binding (hevein) domain of chitin-binding proteins, *e.g.*, class I and IV chitinases, has been isolated from the leaf of Sugar-beet (1-2). The allergenicity of these chitinases was not assessed, and it may well be present only if the plant is stressed.

Two novel, nearly identical antifungal proteins, IWF1 and IWF2, were isolated from Sugar-beet leaves. The proteins were shown to be related to the family of plant non-specific lipid transfer proteins (3).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but has not been reported to occur clinically as yet (4).

Clinical Experience

IgE-mediated reactions

Sugar-beet seed may uncommonly induce allergy symptoms in sensitised individuals, predominantly in occupational settings such as the animal feed industry and farms.

In a prospective open study over 8 months in a group of 10 atopic children with repeated urticaria, based on oral challenge tests along with history, there were 3 cases of allergy to food colourings. Clinical features were mainly skin symptoms,

sometimes associated with GI manifestations which were non specific. Removal of the colorants resulted in the disappearance of the symptoms in a child (Red cochineal) and regression of symptoms in two others (Red cochineal, Red beet) (5). It was not clear whether this is beetroot or sugar beet but both are closely related family members.

Other reactions

The fresh leaf may cause poisoning due to the 1% oxalic acid content. The leaf may also contain dangerous levels of HCN and/or nitrates and nitrites.

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f299 Sweet chestnut

Castanea sativa

Family:	*Fagaceae*
Common names:	Sweet chestnut, European chestnut, Spanish chestnut
Source material:	Shelled nuts
See also:	Chestnut t206

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Allergen Exposure

Geographical distribution

Sweet Chestnut is a shade-tolerant deciduous tree native to southeastern Europe, Asia Minor, and North Africa. Several edible species of Chestnut are grown around world, the 4 main species being Sweet chestnut (*C. sativa*), Chinese chestnut (*C. mollissima*), Japanese chestnut (*C. crenata*), and American chestnut (*C. dentata*). American chestnut has been decimated by parasites. China, Korea and Italy are the world's largest producers of Chestnuts. The principal European producers are Italy, Spain, Portugal, France, and Greece.

The tree can attain a height of 35 m and a trunk diameter of 2 m. The bark is deeply grooved or fissured in a net-shaped (retiform) pattern, sometimes in a spiral. The flowers of both sexes are borne in 10-20 cm-long, upright catkins, the male flowers in the upper part of the tree and the female flowers in the lower part. By autumn the female flowers, in bunches of 2 or 3 (and up to 7), develop into light-green fruit cupules (husks) covered with sharp spines; each cupule usually contains 2 dark, shiny, red-brown nuts and, with the nuts ripened, is shed during October. Trees start to bear nuts when 30-40 years old.

Raw nuts have a bitter taste from tannins, which improves considerably with cooking, developing into a sweet and nutty flavour, with a texture like a firm baked potato - unlike other nuts, which are crunchy. Chestnuts, unlike other nuts, contain very little fat or oil (2-3%), compared to over 50%; they consist mainly of complex carbohydrate (50%) and water (40-45%), with small amounts of protein (5-10%). They contain no cholesterol. They have been part of the staple diet and a major source of complex carbohydrate in Southern Europe, Turkey and Asia for centuries.

Environment

Edible Chestnuts have been grown for culinary purposes for centuries and can be consumed fresh, boiled, grilled, or roasted. They can be frozen or pureed for desserts or confectionery, or used in stuffing or as a garnish. Dried Chestnuts should be soaked in water, cooked, and then treated as fresh.

Traditionally, Chestnuts are roasted over an open fire or in the oven. They can be dried, ground and used as flour in breads and puddings, or as a thickener in soups. The roasted nut can be a coffee substitute. Some notable specialties include porridge (Italy) and Chestnuts preserved in sugar (marron glacé, a French delicacy). The Corsican variety of polenta is made with Sweet chestnut flour. A variety of Corsican beer has Chesnut as one of its ingredients.

Allergens

Chestnut is the third most-prevalent food allergen among both adult and pediatric allergy patients in Korea. At least 21 IgE-binding components have been isolated, and 9 protein bands appear to be major allergens. A heat- and digestion-labile 24 kDa protein with homology to a legume protein of Oak acorn was reported to have the highest binding intensity (1). The 24 kDa component bound to more than 50% of asymptomatic Chestnut-sensitised subjects, with minimal binding in symptomatic Chestnut-sensitised subjects; and a component of 29 kDa bound to more than 50% of symptomatic Chestnut-sensitised subjects, with minimal binding in asymptomatic Chestnut-sensitised subjects. A later study further evaluated these 2 components, the 24 and 29 kDa allergens. Simulated gastric digestion decreased IgE binding of the most significant allergens, except the 24 kDa one, while minimal changes were noted to occur through SIF (intestinal enzymes). Boiling treatment could decrease IgE binding components of the most significant allergens, including the 24kDa one (2).

To date, the following allergens have been characterised:

Cas s 5, a chitinase, an approximately 32 kDa protein, a major allergen (3-9).

rCas s 5 (3).

Cas s 8, a Lipid Transfer Protein, a 9.7 kDa protein, a major allergen (10-12).

Cas s 5 belongs to the Class I chitinases, enzymes that contain an N-terminal hevein-like domain homologous to Latex hevein (Hev b 6.02), and a larger catalytic domain. They are the major panallergens in fruits associated with Latex-fruit syndrome (3,5,9). Recombinant Cas s 5 is homologous to its natural counterpart (3).

Although Chestnut allergy is strongly associated with Latex-fruit syndrome, Chesnut allergy may occur independently of this syndrome and has been attributed to the presence of Cas s 8, a Lipid Transfer Protein. In a study of 12 patients sensitised to Chestnut but not to Latex, along with 3 control patients with Latex-Chestnut allergy, a Lipid Transfer Protein was isolated and found to bind to serum-specific IgE in 91% (as shown by IgE immunoblotting) and 58% (as shown by ELISA) of sera from patients with Chestnut but not Latex allergy. Sixty-six percent of these patients had positive skin prick test responses to Cas s 8. Allergenic LTPs from Peach fruit and Artemisia vulgaris pollen were also reactive. In contrast, Avocado class I chitinase and Latex hevein, allergens associated with Latex-fruit syndrome, showed no reaction. The authors suggested that LTPs and class I chitinases can be used as diagnostic tools in patients with Chestnut allergy, to predict whether an associated Latex sensitisation and a risk of cross-reactivity with other plant foods and pollens exist (7).

Cas s 1 and 2 other allergens, an IPR-protein and a profilin, have been isolated from the pollen of European chestnut tree but have not to date been shown to be present in Sweet chestnut (13).

Potential cross-reactivity

Approximately 30-50% of individuals who are allergic to Natural rubber latex (NRL) show an associated hypersensitivity to a number of plant-derived foods, especially freshly consumed fruits (14-17). Some authors have called this the Latex-fruit syndrome, and foods associated include Avocado, Banana, Sweet Chestnut, Kiwi, Peach, Tomato, Potato and Bell pepper (in approximate decreasing order of relevance). Fig, Pineapple and Peanut have also been implicated (18-21). A number of plant protein families have been shown to be involved in Latex-fruit syndrome. Two of these are also pathogenesis-related (PR) proteins. Class I chitinases have been identified as a major category of IgE-binding allergens for patients allergic to NRL. A beta-1,3-glucanase was identified as an important Latex allergen that shows cross-reactivity with proteins of Bell pepper. Another important NRL allergen, Hev b 7, is a patatin-like protein that shows cross-reactivity with its analogous protein in Potato (19). Furthermore, patients with allergy to plant-derived foods and associated pollen allergy show a high frequency of IgE

reactivity to the panallergen profilin. However, whether Latex sensitisation precedes or follows the onset of food allergy has not been resolved (16).

Allergy to Chestnuts has been widely reported in connection to Latex-fruit syndrome. However, few studies address actual allergy to Chestnuts in patients reacting primarily to this food. In this study, 22 consecutive subjects with proven allergy to Chestnut (according to DBPCFC or a convincing history of anaphylaxis) were studied. The age of onset of reactions to Chestnut ranged from 5 to 70 years, with 8/22 (36%) patients having experienced severe anaphylactic episodes. SPTs with Chestnut were positive in 71%, and IgE antibodies were detected in 54% of patients. Eighty-six percent and 59% of patients also had positive responses to pollen and Latex allergens, respectively. Eighteen patients had actual allergy to other foods, of which these were the main ones: Banana, in 45% of patients; Avocado, in 40%; and Hazel nut, in 32%. There was a significant association between sensitisation to Latex and clinical reactivity to Avocado and/or Kiwi ($p<0.01$); while reactivity to Hazel nut was associated with allergy to Peanut ($p=0.003$) and Walnut ($p<0.001$) (22).

In a study of 47 Latex-allergic patients, immunological reactivity to foods was found in 33. Seventeen patients manifested a clinical allergy to at least 1 food, including 11 patients with anaphylaxis and 14 with local sensitivity reactions. Positive food skin tests occurred most frequently with Avocado (53%), Potato (40%), Banana (38%), Tomato (28%), Chestnut (28%), and Kiwi (17%) (19).

Chestnut and Natural rubber latex (NRL) allergy are often associated in Latex-fruit syndrome. This study's aim was to establish whether concurrent NRL and Chestnut IgE antibody reactivity are the results of co-sensitisation or cross-reactivity.

Sera from 19 patients with Chestnut- and NRL-specific IgE were selected and tested for reactivity with recombinant (r) Latex allergens. IgE-antibodies were detected to rHev b 6.01 (prohevein) in 58% of the sera, to rHev b 5 in 32%, to rHev b 12 in 4 of 13 sera, to rHev b 7.02 and rHev b 11 in 4, and to rHev b 1 in 2 of 19 sera. rHev b 8-IgE antibodies were found in 9 sera (47%), whereas 6 displayed monosensitisation to rHev b 8 with regard to the test panel. Three of 16 sera showed IgE to cross-reactive carbohydrate determinants. In most sera recognising rHev b 5 and/or rHev b 6.01 as major allergens, the IgE reactivity to NRL remained unaffected by Chestnut extract, and Chestnut IgE remained unaffected by NRL extract. Conversely, in sera with rHev b 8 as the dominant allergen, IgE-binding to NRL was nearly completely inhibited by Chestnut and vice versa. IgE-binding to rHev b 8 was abolished by Chestnut extract. The study concludes that although patients have concomitant IgE antibody reactivity to Chestnut and NRL, cross-reactivity could be demonstrated mainly in those patients with IgE to Hev b 8 (profilin) from NRL (23).

However, the prevalence of combined NRL and Chestnut allergy may vary according to the population in question and may be very low in some groups. Among 137 patients with NRL allergy, food allergy to Chestnut was reported in only 1 patient. (24) In a Taiwanese screening program to identify Latex-sensitised hospital employees, elevated serum total IgE was found in 22(16.9%) of 130 nurses, 3(16.7%) of whom had increased Latex-specific IgE, further confirmed by SPT determination. No cross-reactive fruit allergy (Melon, Banana, Kiwi, Tomato, or Chestnut) was found among the Latex-sensitised nurses (25).

Of the plant protein families, a Class I chitinase containing an N-terminal hevein-like domain homologous to and cross-reacting with hevein (Hev b 6.02) has been shown to be a major panallergen responsible for Latex-fruit syndrome involving cross-reactivity among Chestnut, Banana and Avocado (5-6,9,14-15,26-28). Class I chitinases have also been detected in Cherimoya, Passion fruit, Kiwi, Papaya, Mango, Tomato, and Wheat flour extracts (29). Cross-reactivity is modulated due to chitinase in the Latex plant (Hev b 11), which displays 70% identity to the endochitinase from Avocado and its hevein domain, and 58% to

hevein in Latex (Hev b 6.02). Hev b 11, a class I chitinase, displays a different IgE binding capacity than hevein (4).

A review of 28 cases of sensitisation to Latex showed that Banana- and Chestnut-induced allergies were the allergies most frequently associated with Latex-induced allergy (30). In a study of 25 patients with Latex allergy (9 [36%] with anaphylaxis), 13 (52%) were found to have concomitant food allergies to a total of 42 foods, of which 23 had caused systemic anaphylaxis. The most frequent food hypersensitivities were to Avocado (n=9), Chestnut (n=9), Banana (n=7), Kiwi (n=5) and Papaya (n=3). Cross-reactivity among Latex, Avocado, Chestnut, and Banana was demonstrated (31).

A report was made of 8 patients allergic to Latex and Fruit (Chestnut and Banana), 4 of whom had experienced anaphylaxis following ingestion of the fruit. In the 6 patients with symptoms after eating Chestnuts, SPT for Chestnut was found in 5. Histamine release to Chestnuts was positive in 3 of the 6. One patient with no skin reactivity to Chestnut, but showing IgE antibodies in serum tests, tolerated the fruit. Other case reports are illustrative of Chestnut allergy. Patient 1, a 32-year-old housewife, experienced itching of the mouth, rhinitis, and facial angioedema 30 minutes after eating a raw Chestnut. Patient 2, a 23-year-old sister of Patient 1, developed itching of the palate, sneezing, nasal discharge and asthma 10 minutes after eating Chestnuts. Patient 4, a 20-year-old housewife, 10 minutes after ingestion of Bananas and Chestnuts, developed asthma, rhinitis and urticaria. Patient 6, a 23-year-old woman student, experienced anaphylactic episodes (general urticaria, angioedema, and asthma) following the ingestion of Chestnuts and Bananas. Patient 7, a 42-year-old housewife, had an anaphylactic reaction after eating Chestnuts. Patient 8, a 17-year-old female student, developed generalised urticaria and angioedema with laryngeal involvement after eating Chestnuts, and ingestion of Banana caused itching of the mouth (32).

Similarly, a report describes an 8-year-old boy, with a number of previous surgical procedures, who developed acute episodes of urticaria following contact with NRL, and then angioedema and dry cough after ingestion of Chesnuts. SPT for Latex and Chestnut was positive. IgE antibodies were detected to Latex but not to Chestnut. Open oral challenge with Chestnut was positive: 15 minutes after ingestion of 0.5 g of Chestnut, he developed bouts of sneezing, dry cough, perioral itching and erythema, and isolated facial wheals (20).

However, not all studies indicate that sensitisation to Chestnut, or cross-reactivity between Latex and Chestnut, is clinically relevant. For example, in a Turkish study investigating the prevalence of Latex and Latex-associated food sensitivities among hospital employees and atopic children – 61 hospital employees and 40 atopic children – allergen-specific IgE evaluation confirmed sensitisation to NRL in 30 subjects, but not all were symptomatic. Chestnut sensitisation was demonstrated in 37, but whether these individuals displayed allergic symptoms for Chestnut was not investigated; yet the implication that sensitisation may occur without allergic expression is apparent (33). Other authors concur, suggesting that serologic tests seem to be of low significance for prediction of food allergy in Latex-allergic patients, and that in many cases, sensitisation occurs with no clinical expression (15,34).

Cross-reactivity has also been described between Avocado and Chestnut. In a study of 17 patients with immediate hypersensitivity to Avocado, common antigenic determinants were shown to exist among Avocado, Latex, Chestnut, and Banana extracts (35). Recent knowledge suggests that the panallergen chitinase may have been responsible.

Although Chestnut allergy is strongly associated with Latex-fruit syndrome, Chesnut allergy may occur independently of this syndrome and has been attributed to the presence of Cas s 8, a Lipid Transfer Protein (7). Cross-reactivity with other foods containing LTPs is therefore possible. In a

study evaluating, by means of SPT, the reactivity to LTPs from Peach, Apple, Chestnut and *Artemisia* pollen, Chesnut LTP was reported to be less cross-reactive than Apple and Peach LTPs. In a group of Peach-allergic individuals, the most frequent pattern of cross-reactivity of LTPs was the combination Peach-Apple (45%), followed by Peach-Apple-*Artemisia*-Chestnut (21%). Significant correlations were found between Peach and Apple LTPs, and between Artemisia and Chestnut LTPs. Positive SPTs to Chestnut LTP were observed only in patients with positive SPTs to *Artemisia* LTP. All the patients with positive case histories to Chestnut reacted to Chestnut LTP. (11) This is in particular relevant in *Rosaceae* fruit-allergic populations in the Mediterranean area, where LTPs have been identified as major allergens, especially in Apple and Peach. Purified LTPs from *Artemisia* pollen and from Chestnut meat have a 43-50% sequence identity with the equivalent allergens of Apple and Peach. A similar degree of sequence identity (50%) was found between the *Artemisia* and Chestnut proteins. Therefore, although LTPs from *Artemisia* pollen and Chestnut cross-react with LTPs of *Rosaceae* fruits, significant differences in specific IgE-binding capacities have been noted among members of the plant LTP family (10).

The study also demonstrated that Latex-allergic patients (23%) recognise a protein with sequence homology to the protein family patatin, known to be an important protein in Potato. Cross-reactivity between Latex and several Potato proteins was observed through immunoblot inhibition analysis (19).

In 4 patients with an allergy to F*icus benjamina*, 2 patients had a cross-allergy to NRL and the associated cluster of tropical fruit (Banana, Kiwi, Avocado, and Chestnut) (36).

The enzymes Papain and Bromelain may share epitopes with Chestnut allergens (14,26).

According to a report of a 4-year-old boy who developed allergic symptoms immediately after peeling and eating an Oak acorn, partial cross-reactivity was demonstrated between Oak acorn and Chestnut (37).

Clinical Experience

IgE-mediated reactions

Allergy to Chestnut on its own is infrequent, considering how common Chestnut consumption is in certain countries (38); but Chestnut allergy is more frequently associated with the complex sensitisation of NRL-allergic individuals to fruits and vegetables (14-17,24). However, it may be that allergy to Chestnut is underreported, since the possibility of allergic disease tends to be insufficiently investigated. In a Korean study evaluating the clinical significance of Chestnut as a food allergen in 1,738 patients with respiratory allergies, skin reactivity to Chestnut was found in 56 (3.2%) (1).

A study investigating the prevalence of NRL sensitisation and allergy in 74 children with atopic dermatitis reported that 12 of the 74 atopic children had IgE antibodies to Latex. Twenty children without proven Latex sensitisation showed increased food-specific IgE, most frequently to Potato, Banana, and Chestnut (39).

Oral allergy syndrome induced by Chestnut, followed by rhinoconjunctivitis and asthma, has been described in a 22-year-old woman. She reported that when chewing Chestnut, she had felt a burning sensation and itching of the oropharyngeal mucosa followed by lacrimation, nasal pruritus, violent sneezing salvos, and “moderate” difficulty in breathing, but not severe enough to require treatment. Symptoms initially had been relatively minor and limited to oral ones, but subsequent episodes became progressively worse. The challenge with fresh food was positive. Skin prick test with a commercial product and the prick-by-prick method with fresh Chestnut were negative. Skin prick testing with a freshly prepared extract of fresh Chestnut, and the passive transfer reaction, were positive. Serum tests were negative (40).

Four cases of nurses with allergy to NRL followed by anaphylaxis to Chestnut were reported. The presence of Chestnut sensitivity was demonstrated by positive SPT, but IgE antibodies to Chestnut were found in only 2, suggesting that anaphylaxis to Chestnut is possible even in the absence of serum IgE

antibodies to Chestnut (41). Anaphylaxis to Chestnut may be classified as "idiopathic" until investigated further (42).

A 4-year-old boy developed ocular itching, eyelid and lip angioedema, unproductive cough, wheezing and dyspnoea immediately after peeling and eating an Oak acorn. Months later, he experienced similar symptoms after eating a Chestnut. He tolerated Latex and Banana. SPT was positive to Oak acorn peel and Chestnut, and negative to the pollen. The IgE antibody level was raised for Chestnut and Oak acorn peel, with a degree of cross-reactivity demonstrated between these foods (37).

Chestnut has been reported to cause urticaria-angioedema in a 29-year-old man (43).

Other reactions

Chestnut tree pollen is an aeroallergen (44).

The Horse chestnut, *Aesculus hippocastanum*, is an entirely different tree from the Sweet chestnut. The Horse chestnut is not edible; its burs have blunt spikes, while Sweet chestnut burs are very sharp and spiny.

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Juglans regia

Family: *Juglandaceae*

Source material: Shelled nuts

See also: Walnut t10

The *Juglandaceae* family contains 2 important genera: Hickory/Pecan (*Carya*) and Walnut (*Juglans*). Walnut is the common name for 20 species of deciduous trees in the *Juglans* genus (native to south-western Asia, eastern Asia, and the Americas). Those species have been separated into 4 taxonomic sections: *Dioscaryon* (English walnut), *Rhysocaryon* (Black walnut), *Cardiocaryon* (Asian butternut), and *Trachycaryon* (American butternut). Section *Dioscaryon* contains a single species, *J. regia*, and this nut is commonly called the English walnut or Persian walnut. Section *Rhysocaryon* includes all of the Black walnuts: for example, the species *J. nigra* (Eastern black walnut), *J. californica* (Southern California black walnut), *J. hindsii* (Northern California black walnut), *J. major* (Arizona black walnut) and J. *microcarpa* (Texas black walnut). Section *Cardiocaryon* contains *J. ailantifolia* (Japanese walnut), *J. cathayensis* (Chinese walnut), and *J. mandshurica* (Manchurian walnut), among others. Section *Trachycaryon* comprises a single species native to North America, *J. cinerea*, known as the Butternut or White walnut. Within some species there are also different cultivars (1)

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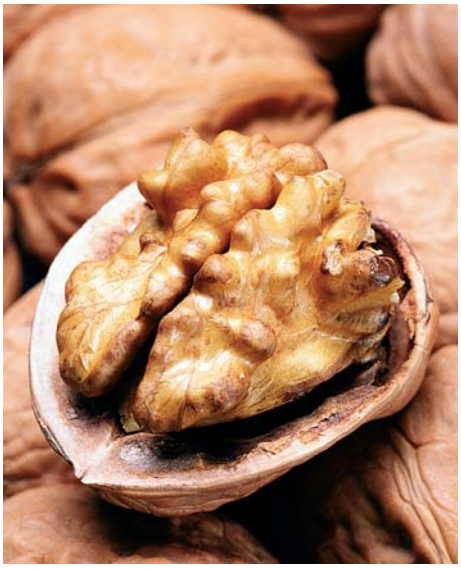

Allergen Exposure

Geographical distribution

Walnut is one of the most important nut crops. The leading commercial producers of Walnuts are the United States, Turkey, China, Iran, France and Romania.

The Walnut tree is up to 20 m tall, with a large, spreading, rounded top and thick, massive stem. Walnut trees are monoecious, with male flowers borne in long, unbranched, drooping catkins, and female flowers borne singly or in short spikes. The leaves and outer green husks are poisonous to fish and most animals. The flowers appear in May, and the yellow leaves turn green by mid-June.

The Walnut fruit is a nut, borne singly or in pairs and enclosed in a solid, non-splitting green husk. The fruit is oval in shape, 4 to 5 cm across. The outer, slightly soft coat, which is called a husk or shuck, is shiny and green at first. It changes to dark brown when it is ripe. Inside this fruit is a single seed, the Walnut, which has an edible, oil-rich, white, two-lobed, wrinkled kernel enclosed in a thick, hard, ridged, and brown to black shell. In mid-September the nuts can be harvested with their husks still on. By October, the husks fall off, and the hard-shelled nuts can be gathered.

Walnut shells are composed of 2 halves. Between the halves is the “shell seal”, which is usually tight, to protect the nut from moisture and pests. But the shell of freshly picked Walnuts can easily be cracked open by hand. After washing and drying, the shell becomes very hard and must be broken open with a tool such as a nutcracker or hammer.

f256 Walnut

A hard, fibrous membrane lines the inside of the shell, runs between the two halves of the nut, and is removed before eating. The Walnut itself is covered by a thin edible skin called the pellicle, which can be removed by blanching the nut in rapidly boiling water for 30 to 60 seconds. The pellicle contains tannins; the darker the pellicle, the more tannins it contains. Walnut has a very high polyunsaturated fat content, which makes the nut extremely perishable, requiring careful storage.

While there are numerous species of edible Walnuts, the 3 main ones consumed are the English (or Persian) walnut (*J. regia*), the Black Walnut (*J. nigra*), and the White (or Butternut) Walnut (*J. cinerea*). The English walnut is the most popular and features a large nut and thinner shell, which is easily broken with a nutcracker. The Black walnut has thicker shells that are harder to crack; the nuts are oilier and richer-tasting, with a much more pungent and distinctive flavour than that of the English walnut. They are harder to extract from the shell in large pieces. The much less available White walnut has a sweeter and oilier taste than the other 2 types, and very high protein content.

Environment

The nuts are rich in oil, particularly in alpha-linoleic acid (omega 3 fatty acid) and linoleic acid (polyunsaturated fatty acids), and are widely eaten both fresh and in cookery. Walnuts can be eaten directly from the shell, but more often they are eaten as an ingredient in baked goods, ice cream or other foods. They are used in salads and in meat, poultry, fish and pasta dishes. Immature young fruits are pickled in vinegar and considered a delicacy. A liqueur is made in France from the husks. Greeks and Romans used Walnuts to cure headaches, because of the shape, which resembles the two halves of the brain.

The oil is used in salads and pasta. The allergenicity of this oil and various other gourmet nut oils depends on the extraction method and the purity of the end product (2).

Oil paint often contains Walnut oil as an effective binding medium, known for its clear, glossy consistency and non-toxicity.

Walnut husks can produce a rich yellow-brown to dark brown dye that is used for dyeing fabric and for other purposes. Husks should be handled wearing rubber gloves, to avoid dyeing one's fingers.

Allergens

The following allergens have been characterised:

Jug r 1, a 14-16 kDa protein, a 2S albumin, a major allergen (1,3-9).

Jug r 2, a 44-48 kDa protein, a 7S vicilin globulin, a major allergen (1,3,5-7,10).

Jug r 3, a 9 kDa protein, a lipid transfer protein, a major allergen (5-7,11).

Jug r 4, a legumin-like protein. (5-6,12-13).

Jug r profilin (14).

Jug r 1, a 2S albumin, was shown to be a major allergen in a study of 20 American Walnut-allergic individuals; the allergen bound 75% of the patients' sera (4). Similarly, IgE binding to Jug r 1 was demonstrated in 12 of 16 (75%) sera from Walnut-allergic patients (3). The IgE binding inhibition study suggested that the Walnut 2S protein precursor undergoes post-translational modification into a large and a small subunit similar to Castor seed, Cottonseed, Mustard seed, and Brazil nut 2S seed storage protein allergens (3).

However, contrasting results were seen in a study of 46 Italian patients, either with oral allergy syndrome confirmed by open oral challenge, or with systemic symptoms after ingestion of Walnut; a comparison of the Walnut IgE binding profile in patients with and without pollen allergy showed that the only major allergen recognised was a lipid transfer protein (LTP) (Jug r 3), which was recognised by 36 patients (78.2%). Two other minor allergens of approximately 9 kDa, both belonging to the vicilin family, were recognised by 10 patients (21.7%). Nine patients reacted to vicilin A, and 1 patient to vicilin B (which has 90% homology with Cocoa). Two patients exclusively allergic to

Walnut were sensitised to vicilin A. IgE binding to Walnut LTP was completely inhibited by Peach LTP. The study concluded that in the Italian population, the LTP is a major allergen (7).

Jug r 4 has been shown to be a major allergen and was found in sera from 15 of 23 (65%) Walnut-allergic patients. (12) rJug r 4 has been cloned and was demonstrated to bind to serum IgE antibodies from 21 of 37 (57%) Walnut-allergic patients (13).

Allergens similar to the English walnut allergens Jug r 1 and Jug r 2 have been shown to be present in Walnuts of other closely related *Juglans* species (1). However, although cross-reactivity between the Jug r 1 allergen and a similar allergen in other *Juglans* species occurs, and appears to be extensive, species other than *J. regia* were shown to be unable to completely inhibit binding to the recombinant form of Jug r 1. The authors suggest that perhaps the other species had less 2S albumin and left more Jug r 1-specific IgE antobodies available in solution for binding to the immobilised rJug r 1, or that binding affinities differ slightly. They also proposed that the reduction and partial linearisation of rJug r 1 by the SDS in the gel or the non-natural folding of a precursor fusion protein (the 2S albumin precursor is normally processed into large and small subunits in Walnut) introduces additional IgE epitopes that are still present when membrane-bound. The authors suggested that, in any case, subtle differences in the 2S albumins can be inferred (1).

Potential cross-reactivity

A high degree of cross-reactivity occurs among the different Walnut species (1).

Early inhibition studies suggested cross-reactivity between Walnut and Pecan when 7 tree nuts (Walnut, Pecan Almond, Hazel nut, Brazil nut, Cashew, Pistachio) and Peanut were evaluated (15). Other studies have also reported a higher risk of cross-reactivity between Walnut and Pecan (16) and among Walnut, Pecan, and Hazel nut (17). The allergens resulting in this relationship were not elucidated. Cross-reactivity among Walnut, Hazel nut and Brazil nut was reported in a patient with Walnut-induced anaphylaxis (18).

A high degree of cross-reactivity among the tree nuts is most likely to be a result of the 2S albumin and other storage proteins. Jug r 1 has been shown to have a 46.1% identity with the Brazil nut 2S albumin Ber e 1 (3). A major allergen in Cashew nut, a 2S albumin, was reported to be the possible basis for cross-reactivity with Walnut 2S albumin (19). Cross-reactivity among the 2S albumin in Almond, Walnut and Hazel nut has been demonstrated (20).

There are reports of cross-reactivity among allergens in Sesame and allergens in Walnut (21). This may occur as a result of the presence of a 2S albumin (Ses i 2) or a 7S vicilin-type globulin (Ses i 3) found in Sesame seed; both kinds of storage proteins are found in Walnut (22). Other studies have reported that the Sesame 11S globulin shows only partial immunological cross-reactivity with Walnut (23).

Vicilin allergens of Peanut (Ara h 1), Walnut (Jug r 2), Hazel nut (Cor a 11) and Cashew nut (Ana o 1) share structurally related IgE-binding epitopes, and authors have suggested that avoidance or restricted consumption of other tree nuts should be recommended to Peanut-sensitised individuals (9). Ana o 1, a 7S vicilin-like globulin from Cashew, has a 52-62% similarity to Walnut (6). A 19 kDa protein of Buckwheat has been shown to have a weak homology to the vicilin-like protein of Walnut (Jug r 2), Cashew (Ana o 1), and to 7 S globulin from Sesame seed (24). A 7S globulin from Coconut has also been shown to be cross-reactive with Walnut and Hazel nut (25).

Linear IgE-binding epitopes identified in legumin allergens of Peanut (Ara h 3) and other allergenic tree nuts (Jug r 4 of Walnut, Cor a 9 of Hazel nut, Ana o 2 Cashew nut) were mapped.

Conformational analysis has shown that the legumin allergens of Peanut (Ara h 3), Walnut (Jug r 4), Hazel nut (Cor a 9), and Cashew nut (Ana o 2) have consensual surface-exposed IgE-binding epitopes that exhibit some structural homology, which accounts for the IgE-binding cross-reactivity

observed among Peanut and tree nut allergens. IgE-binding epitopes similar to those found in 11S globulin allergens do not apparently occur in other vicilin allergens with the cupin fold, as in Peanut (Ara h 1), Walnut (Jug r 2), Hazel nut (Cor a 1), and Cashew nut (Ana o 3) (26).

Jug r 3 from Walnut is a lipid transfer protein. As LTP-hypersensitive patients experience adverse reactions after ingestion of botanically unrelated plant-derived foods as well, in view of the high prevalence and severity of the reactions, authors have recommended that Hazel nut, Walnut, and Peanut should be regarded as potentially hazardous for these patients (7,11). In a study of 20 LTP-monosensitive patients with a clinical history of allergic reactions following the ingestion of *Rosaceae* fruits (Apple, Pear, Peach, Cherry, Apricot, Plum, or Almond), 80% reported clinical reactivity to nuts (Hazel nut, Walnut, Pistachio); in 11 cases (55%) nuts caused systemic symptoms, with urticaria/angioedema in 9 cases and anaphylaxis in 2. Maize and beer were not tolerated by 4 (20%) and 2 (10%) respectively. After ingesting Grapes, 2 patients experienced immediate gastro-enteritis/rhinitis and oral allergy syndrome, respectively. Cashew and Pistachio induced an anaphylactic reaction in a single patient, but Cashew is rarely eaten in Italy. Only 2 patients had ever eaten Pistachio, and 1 reacted; hence the study conclusion that these 2 nuts may be significant LTP-containing foods for adverse reactions (11). The relevance of LTP in cross-reactivity among Walnut and other LTP-containing foods, *e.g.*, Apple (Mal d 3), has been reported (27).

Jug r 4, a legumin-like protein, has been shown to have significant sequence homology to Hazel nut and Cashew legumin allergens, and *in vitro* cross-reactivity was demonstrated with Hazel nut, Cashew, and Peanut protein extracts (13). Legumin-like seed storage proteins have been implicated in cross-reactivity between Coconut and Walnut, Almond and Peanut (28).

Walnut profilin may result in cross-reactivity with other profiling-containing food, but this has not been established yet.

Clinical Experience

IgE-mediated reactions

Tree nuts and Peanuts are frequent causes of severe IgE-mediated food hypersensitivity and anaphylaxis. In particular, tree nut allergies are potentially life-threatening, rarely outgrown, and appear to be increasing in prevalence. Peanut and tree-nut allergic reactions coexist in a third of Peanut-allergic patients, frequently occur on first known exposure, and may be life-threatening (29).

The frequency of Walnut allergy in children with IgE-mediated food allergy has been reported as 4.2% (30). Walnut was most commonly reported to be allergenic by participants in the Food Allergy and Anaphylaxis Network (FAAN) Peanut and Tree Nut registry in the United States. A questionnaire of 5,149 patients (mainly children) found that of allergic reactions to tree nuts, 34% of reactions were to Walnut (31). In 1,000 British patients allergic to nut, 30 cases of severe allergic reactions to Walnut occurred (32). Random telephone surveys found that the importance of Walnut allergy and other nut allergies is related not only to the severity of the allergic reactions but also to the high prevalence in the general population, estimated to be around 0.2% to 0.7% (33-34). In a SPT study of 1,286 allergic patients, aged 2-79 years, in the southeast part of Iran, it was found that 30.33% of the subjects were sensitised to Hen's egg, 29.16% to Walnut, 21.46% to Cow's milk, 19.21% to Beef, and 15.32% to and Hazel nut (35).

As Walnuts are promoted as part of a healthy diet because of their polyunsaturated fat and antioxidant content, consumption of Walnuts and the addition of them to processed foods can be expected to increase.

In a study based on a patient questionnaire, hypersensitivity to Walnuts was shown to be more common in patients with Birch pollen allergy (26%) than in patients without Birch pollen allergy (6%) (36). Similarly, in a study of grass pollen allergy in Northern Italy, where this allergy is the most common, IgE antibodies to Bet v 1 were more strongly associated with nuts and

legumes, while Bet v 2 was more strongly related to allergy to fresh fruits and vegetables (37).

Anaphylaxis to Walnut has been frequently reported. In a case series, 10 of 32 fatal anaphylactic reactions to foods resulted from ingestion of a tree nut, and Walnut was named in 3 cases (38). In the United Kingdom register of anaphylaxis deaths between 1992 and 1998, 37 food-induced fatalities were recorded, 5 caused by Walnut (39-40). Of 55 severe or fatal food-allergic reactions reported in a British paediatric population, 1 near-fatal reaction was caused by Walnut (41). Nevertheless, the prevalence of severe allergy may vary according to population groups. In a retrospective review of 213 Australian children with Peanut or tree nut allergy, there was only 1 reported case of anaphylaxis to Walnut alone, and 3 to a mixture of nuts (42).

Walnut-induced anaphylaxis was reported in an 11-year-old boy who developed gastric pain followed by severe asthma, generalised urticaria and collapse 15 minutes after eating home-baked cookies made with Walnuts, Pistachios, dried Figs and raisins. Skin reactivity and IgE antibodies were detected to Walnut and Hazel nut (18). Significantly, accidental intake of foods containing small amounts of Walnuts not listed on the food labels can induce anaphylaxis (43).

In particular, patients with an initial diagnosis of “idiopathic” anaphylaxis may have in fact reacted to Walnut. A hundred and two patients with an initial diagnosis of idiopathic anaphylaxis were evaluated with 79 food allergens using SPT; only those patients were included whose episodes consisted of at least 2 of the following: angioedema with or without urticaria, laryngeal oedema leading to severe dyspnoea, hypotension, and loss of consciousness; 32 patients (31%) had positive tests to 1 or more foods. Walnut was among the foods implicated. The authors concluded that some instances of “idiopathic” anaphylaxis are not truly idiopathic (44).

Importantly, delayed anaphylaxis to Walnut following epinephrine administration may occur, as documented in a 7-year-old girl with known Walnut allergy. Five minutes after the accidental ingestion of a bite of a Walnut-containing salad, the patient's mother injected her with 0.15 mg epinephrine, although no clinical reaction was noted prior to administration. After 90 minutes of observation, she suddenly developed diffuse pruritus, cough, wheeze, erythema, and urticaria. Further treatment resulted in resolution of symptoms (45).

Walnut food-dependant exercise-induced anaphylaxis has been reported (46-47).

Cross-reactivity may have severe consequences. An 18-year-old male experienced generalised urticaria, angioedema of the face, wheezing, dyspnoea and hypotension a few minutes after eating a cake containing Walnut. He had previously experienced episodes of urticaria and oral itching after eating Walnuts. During SPT evaluation for Walnut and Brazil nut allergy, a severe episode of anaphylaxis occurred immediately after pricking with fresh Brazil nut. The subject had never eaten Brazil nut before. The authors hypothesise that this adverse reaction was a result of cross-reactive mechanisms (48).

Anaphylaxis to Walnuts and Pine nut induced by angiotensin-converting enzyme inhibitors (ACE) has been described (49).

Although the storage proteins are in general major allergens responsible for adverse reactions to Walnut, in Italian patients the lipid transfer proteins are major allergens and responsible for oral allergy syndrome. In a study of 46 Italian patients either with oral allergy syndrome confirmed by open oral challenge or with systemic symptoms after ingestion of Walnut, the only major allergen recognised was a lipid transfer protein that bound serum of 37 patients. Two other minor allergens, both belonging to the vicilin family, were recognised by 10 patients. IgE binding to Walnut LTP was completely inhibited by Peach LTP, and the authors suggested that the sensitisation to this protein seemed to be secondary to the sensitisation to Peach

LTP, which would act as the primary sensitiser. Symptoms of oral allergy syndrome were reported in 24 patients, gastrointestinal symptoms in 1, glottic edema in 13, urticaria in 6, angioedema in 8, shock in 10, atopic dermatitis in 2, and asthma in 1 (7). The importance of lipid transfer proteins in Walnut-allergic patients has been reported in other studies (11,18).

Walnut allergy may occur as part of a true multifood allergy. A 4-year-old male, who first experienced urticaria and asthma related to the ingestion of eggs at the age of 2, in subsequent years developed rhinitis, angioedema, headache, and gastroenteritis. Symptoms started between a few minutes to 2 hours after the ingestion of a number of foods. SPT and IgE antibody determinations were positive for a number of foods, including Walnut, and this was confirmed by DBPCFC (50).

Walnut may also exacerbate atopic dermatitis. Over half of paediatric patients with atopic eczema were found to be have IgE antibodies to Walnut (51).

Occupational contact urticaria from Walnut associated with hand eczema has been reported (52).

Other reactions

Juglone is the active ingredient of the green flesh of Walnuts and is known to be a strong irritant. Two young nursery-school playmates developed contact pigmentation and acute irritant contact dermatitis as a result of contact with the "juice" of green Walnut husks (53).

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Triticum aestivum

Family:	*Poaceae* (*Gramineae*)
Common names:	Wheat, Common wheat, Bread wheat
Synonyms:	*Triticum hybernum L., Triticum macha Dekap. & Menab., Triticum sativum Lam., Triticum sphaerococcum Percival, Triticum vulgare Vill*
Source material:	Untreated planting seeds
See also:	Cultivated wheat g15, Gluten f79 and rTri a 19; Omega-5 Gliadin f416

The following are important varieties of Wheat:

Common Wheat – *Triticum aestivum L.*
Club Wheat – *T. aestivum compactum*
Durum Wheat, Macaroni Wheat – *T. durum*
Spelt Wheat – *T. spelta L.*
Rivet Wheat – *Triticum turgidum L.*
Emmer Wheat – *T. dicoccoides*
Poulard Wheat – *T. turgidum L.*
Polish Wheat – *T. polonicum L.*
Persian Wheat – *T. carthlicum Nevski*
Oriental Wheat – *T. turanicum Jakubz.*
Einkorn Wheat – *T. monococcum L.*
Wild Einkorn Wheat – *T. boeoticum Boiss*

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Allergen Exposure

Expected exposure

Wheat is one of the major cereal grains belonging to the grass family (*Poaceae* or *Gramineae*) and is a staple food item in most diets worldwide.

Wheats are freely tillering, usually robust grasses 60 - 120 cm tall. The inflorescence has a typical single spike on each node. There are very many distinct types of Wheat that have been named as species. They are separable into three groups – diploid, tetraploid and hexaploid, according to the number of sets of chromosomes. The most important Wheats today are hexaploids, having 6 sets. These Wheats are in most cases larger and higher-yielding than diploids and tetraploids, and they also adapt to a wider range of climates.

The hexaploid *Triticum aestivum* is by far the most important of all Wheat species, the highest yielding and the widest ranging, as well as the one most suited to bread making. Its centre of origin is thought to be somewhere south of the Caspian sea, but its rise to prominence came only after Wheat cultivation had spread to more humid areas. During the last 2,000 years, it has come to replace almost all other species and has spread to almost all parts of the world where Wheat can be grown.

All varieties pf Wheat contain soluble and insoluble (gluten) proteins. The softer Wheat with the lowest protein content is used for biscuits, cakes and pastry. This is *T. aestivum* and the varieties closest to it. Harder Wheat with higher protein content is used for bread, semolina, cous-cous, macaroni and pasta. *T. durum* (Durum wheat) is a source of Italian pasta, Indian chappatis and Chinese noodles.

f4 Wheat

Environment

Common Wheat, the best known and most widely cultivated of the Wheats, is cultivated for the grain and used whole or ground. It is processed into Wheat berries or kernels, Wheat bran, Wheat flakes, flour, and Wheat germ. Finely ground, it is the source of flour for the world's softer bread-stuffs, such as cakes. Harder Wheat, on the other hand, is much better suited for breads, and for pastas and other products that need to maintain texture and flavour under the stress of heat. Wheat also is the source of alcoholic beverages such as beer, and the industrial alcohol is made into synthetic rubber and explosives. Bran and germ from flour milling are also important in livestock feed, and the grain itself is fed to livestock whole or coarsely ground. Wheat starch is used for pastes and sizing textiles. The straw is made into mats, carpets, and baskets, and is used for packing material, cattle bedding, and paper manufacturing. Some Wheat is cut for hay. Wheat is sometimes grown for pasture.

Unexpected exposure

See under Environment.

Allergens

Wheat, like all other foods, contains a number of proteins: over 300 have been matched to established protein database information (1), and some have been identified as allergens. The types and proportions of proteins in a cereal have a major impact on the quality and end use properties of the cereal. The major proteins in Wheat vary in proportion according to the type of Wheat, and this variability is one reason reactions to different Wheat products are not consistent.

Wheat protein can be classified into different proteins:

- albumins (water-soluble; not similar to egg or milk albumin)
- globulins (salt-soluble, water-insoluble)
- glutens (composed of gliadin and glutelin, the water/salt-insoluble wheat proteins)

Glutens can be further divided into:

- gliadins (28-42%; the major prolamin protein in Wheat, soluble in 70-90% alcohol)
- glutenins (42-62.5%; the major glutelin proteins in Wheat, soluble in dilute acid or alkali solutions)

Wheat flour contains between 7% and 12% gluten proteins by weight. All gluten proteins are high in proline and glutamine contents, and that is the predominant basis for calling them prolamins. Cereal prolamins have no known function apart from storage. Prolamins consist of a heterogeneous mixture of proteins of a molecular weight 30-90 kDa (2). There are specific names for individual prolamins from different species: secalins from Rye, hordeins from Barley, zeins from Maize, and avenins from Oats.

The 70% ethanol-soluble gliadins of a single Wheat grain can be separated into up to 50 components and are a heterogeneous mixture of single-chained polypeptides. They are divided into 4 groups, here in descending order of mobility in accordance with acid-PAGE studies: alpha-, beta-, gamma-, and omega-gliadins (3). Their molecular weight ranges from around 30 to 75 kDa.

The 70% ethanol-insoluble glutenins are divided into high-molecular-weight (HMW) and low-molecular-weight (LMW) glutenins.

Another way of classify the prolamins is by sequence information into three groups: sulphur-poor (S-poor), sulphur-rich (S-rich), and high-molecular-weight (HMW) prolamins. The S-poor prolamins comprise the omega-gliadins. The S-rich prolamins are the major group of prolamins in Wheat and they comprise the alpha-gliadins, the gamma-gliadins and LMW glutenins. The HMW prolamins play an important role in determining the bread making quality of Wheat. HMW prolamins are also present in Barley and Rye, where they are called D hordein and HMW secalins, respectively.

The following is a list of the type of prolamin in each grain and the percentage that the prolamin contributes to the grain's protein content:

Wheat:	Gliadin	69%
Corn:	Zein	55%
Barley:	Hordein	46-52%
Sorghum:	Kafirin	52%
Rye:	Secalinin	30-50%
Millet:	Panicin	40%
Oats:	Avenin	16%
Rice:	Orzenin	5%

Data suggest that the different prolamins may share regions of amino acid sequence homology with each other and with some of the water/salt soluble albumin/globulin proteins (4).

Early studies demonstrated that a number of Wheat allergens play diverse roles in allergy to Wheat: their sizes include 12, 15, 16, 17, 21, 26, 27, 30, 33, 38, 47 and 69 kDa (5-10).

The water/salt-soluble albumins and globulins are important proteins contributing to immediate hypersensitivity reactions (such as baker's asthma) to Wheat protein in those exposed in an occupational setting (6-7,11) In such cases, these proteins exhibit about 70% to 80% of the allergen-specific IgE-binding activity (7,12-13). They are also important in atopic dermatitis (13-14). Nevertheless, although up to 70 different IgE-binding proteins can be demonstrated to exist in the water/salt-soluble Wheat fraction, only a few of these allergens have been identified and characterised on a molecular basis (15). To the latter belong various 14- to 17-kDa proteins of the alpha-amylase/trypsin inhibitor family, including subunits of the tetrameric alpha-amylase inhibitor (9), 2 highly homologous dimeric alpha-amylase inhibitors (9,15-17) the monomeric alpha-amylase inhibitor (9,16) and a homologue to a barley trypsin inhibitor (16). In a study, the highest *in vivo* allergenic activity was shown to a glycosylated subunit CM 16* of the tetrameric alpha-amylase inhibitor, with skin reactivity detected to this allergen in 14 of 31 patients allergic to Wheat flour. A 36 kDa Wheat glycoprotein with peroxidase activity and similarity to a Barley seed-specific peroxidase has also been isolated from 6 of 10 patients with Wheat allergy and baker's asthma demonstrating specific IgE to this enzyme (70).

Other proteins in the water/salt-soluble fraction, such as peroxidase, glycerin-aldehyde-3-phosphate dehydro-genase, serpin (a serine proteinase inhibitor), and triosephosphate isomerase, have been regarded as major allergens in patients with baker's asthma, but great inter-individual variation of IgE-binding patterns of Wheat flour proteins in baker's asthma has been shown (16,18-19). Other Wheat allergens similar to the 27 kDa acyl-CoA oxidase variants of Rice and Barley or to 39 kDa fructose-bisphosphate-aldolase in Maize and Rice have been identified in pooled sera from Wheat-allergic individuals, but their frequency of sensitisation was not evaluated (15,18,20).

Although the albumin and globulin fractions are the most prevalent allergens in Wheat-allergic individuals, IgE binding has been demonstrated to both gliadin and glutenin fractions (13).

LMW glutenin, alpha-gliadin, and gamma-gliadin have been identified as allergens in Wheat-allergic patients (21). Alpha-gliadin and omega-gliadin (*e.g.* fast omega-gliadin) have been reported to be the allergens associated with baker's asthma (2). LMW glutenin has been reported to be the major allergen for patients allergic to Wheat (22-23). Other studies have shown that alpha-gliadin and gamma-gliadin, in addition to LMW glutenin, are allergens for patients with Wheat allergies (21).

The following allergens have been identified and characterised:

Tri a 12, a profilin, an actin-binding protein, found in Wheat seed and pollen (24-27).

Tri a 14, a lipid transfer protein, resulting in allergic reactions via ingestion, skin contact, and inhalation of Wheat flour (24,28-32).

Tri a 18, a hevein-like protein (24-25).

Tri a Gluten, also known as Gluten, Gliadin, Gamma-gliadin, Omega-gliadin (21,23,33-46).

Tri a Chitinase, a chitinase (47).

Tri a Bd 17K, an alpha-amylase inhibitor CM16 (48-49).

Tri a 25, a thioredoxin (24-25,50-51).

Tri a 26, a glutenin.

Tri a aA/TI, an alpha-amylase / trypsin inhibitor, an approximately 14-15 kDa low-molecular-weight (LMW) allergen, resulting in allergic reactions via ingestion, and inhalation of Wheat, *e.g.*, as flour (5,9,16,52-54).

Tri a Bd36K, a peroxidase purified from Wheat albumin and an inhalant allergen. A 36 kDa protein (19).

Tri a LMW Glu, a glutenin (24,34,46,55-60).

Tri a Germin, a germin (61).

Tri a Peroxidase, a peroxidase (62).

Tri a TPIS, a triosephosphate isomerase, an allergen via inhalation in bakers (63).

Tri a alphabeta Gliadin, a gliadin, also known as gliadin or gluten, resulting in allergic reactions via inhalation of Wheat, *e.g.*, as flour (64).

Tri a alpha Gliadin, a gliadin, also known as gliadin, gluten (2,21,25,33-35,46,55,60,65-66).

Tri a beta Gliadin (2,34,46,60,65-66).

Tri a gamma Gliadin (2,21,33-34,41-42,46,55,57,60,65).

Tri a omega-2 Gliadin (2,33-34,37,46,55, 65-66).

The following allergens have been characterised in Wheat pollen: Tri a 1, Tri a 2, Tri a 3, Tri a 4, Tri a 5, Tri a CBP and Tri a 12. Tri a 12, a profilin, is also found in Wheat seed. (See Cultivated wheat g15.)

Tri a 14, a lipid transfer protein, has been shown to be heat-stable and to lack cross-reactivity to grass pollen allergens. In a study of sera of 16 Wheat challenge-positive patients and 6 patients with Wheat anaphylaxis recruited from Italy, Denmark and Switzerland, LTP was a major allergen only in Italian patients (58). In a study of 40 patients with occupational baker's asthma resulting from Wheat flour inhalation, IgE antibodies to Tri a 14 was found in 60% of 40, and the purified allergen elicited positive skin reactions in 62% of 24 of these patients. Tri a 14 and Peach LTP, Pru p 3, showed a sequence identity of 45%, but the low cross-reactivity between the 2 allergens detected in several individual sera reflected great differences in their 3-dimensional IgE-binding regions (28).

Tri a Gluten is composed of gliadin and glutelin, *i.e.*, the gliadin and glutenin proteins form a "complex" and have been termed Gluten. Originally thought to be a single protein, gliadin is now known to consist of a number of isoforms or unique proteins, *e.g.*, Tri a alphabeta Gliadin, Tri a alpha Gliadin, Tri a beta Gliadin and Tri a omega-2 Gliadin. See below for individual descriptions. Wheat flour contains between 7% and 12% Gluten proteins by weight. By definition, Gluten is found only in Wheat, although the term is commonly used to refer to any similar prolamin protein in any grain that is harmful to a person with coeliac disease. Other grains such as Rye, Barley, Oats and triticale (a Wheat-Rye hybrid) each contain their own prolamin, which causes the same intestinal damage in coeliac disease that gliadin causes. This is due to the similarity in protein structure. See Gluten f79.

Enzymatic hydrolysis of Wheat gluten demonstrated that the polymeric glutenin and monomeric gliadin in the gluten complex showed different behaviour after enzymatic hydrolysis: the monomeric protein (gliadin) and soluble glutenin were prone to enzymatic hydrolysis, while insoluble glutenin was resistant to enzymatic hydrolysis (67).

Tri a 19 (omega 5-gliadin) has been reported to cause sensitisation for between approximately 66% and 92% of Wheat-allergic patients. It has been reported to be a major allergen in Wheat-dependent exercise-induced anaphylaxis (WDEIA) (33).

Tri a 25, a thioredoxin, was reported to be an allergen in 8 out of 17 patient sera. The authors speculated that this family of allergens might play a role in the maintenance of allergic inflammation in baker's asthma (25). A more recent publication questioned whether this protein is a true allergen, since it had been found that thioredoxin alleviates the allergic response and that there was no evidence that thioredoxin acted as an allergen (68).

Tri a 26, a glutenin subunit, and Wheat omega-5 gliadin have been reported as major allergens in Wheat-dependent exercise-induced anaphylaxis. In a study, 29 of 30 patients with Wheat-dependent exercise-induced anaphylaxis had IgE antibodies to these epitope peptides. Twenty-five patients with atopic dermatitis who had IgE antibodies to Wheat and/or Gluten had very low or nonexistent levels of epitope peptide-specific IgE antibodies, suggesting that measurement of IgE levels specific to omega-5 gliadin (Tri a 19) and Tri a 26 is useful for the assessment of patients with Wheat-dependent exercise-induced anaphylaxis (55).

Tri a aA/TI is an alpha-amylase/trypsin inhibitor. This glycosylated form of alpha-amylase inhibitor may be more potent than the non-glycosylated form (8-9). This is a sensitising allergen whether it is ingested or inhaled, having been implicated as a major allergen associated with baker's asthma (9), and, less commonly, with food allergy (69). In particular, the subunits of the tetrameric alpha-amylase inhibitor, CM2, CM3 and CM16, are known to be major allergens for baker's asthma. In Japanese patients with atopic dermatitis, serum IgE bound only to CM3 and not to CM2 or CM16, suggesting that CM3 may be involved in both atopic dermatitis and baker's asthma (52).

Tri a Bd 36K, a peroxidase, is an allergen via inhalation (19).

Tri a LMW Glu appears to be a major allergen. In sera of 28 patients with food allergy to Wheat, 60% of sera were shown to have IgE antibodies against alpha- and beta-gliadins and LMW glutenin subunits (Tri a LMW Glu); 55% against gamma-gliadins; 48% against omega-gliadins; and 26% against HMW glutenins (46).

Tri a Germin is a germin, a glycoprotein expressed in many plants in response to biotic and abiotic stress. Wheat germin (expressed in transgenic tobacco plants) bound IgE from 6 of 12 patients sensitised to Wheat, and elicited skin- reactions in 4 out of 5 cases (61).

Tri a Peroxidase occurs in Wheat (*T. aestivum*). This 36 kDa seed-specific peroxidase is found specifically in *T. monococcum* but is also present in flour from diploid, tetraploid (pasta) and hexaploid (bread) Wheats. Sensitisation occurs via inhalation. Sera from 6 out of 10 patients hypersensitive to Wheat flour were shown to have IgE antibodies directed to this allergen (70). This allergen is one of the most reactive with some patients' sera (14).

Tri a TPIS, a triosephosphate isomerase, is an allergen via inhalation, mainly in bakers (63).

Tri a alphabeta Gliadin has been shown to be present in sera of 12% of bakers with occupational asthma, and it was demonstrated that water-insoluble proteins might also represent causative allergens (64).

Tri a alpha Gliadin, an alpha-gliadin, appears to be a major allergen and was reported to be present in 60% of sera of 28 patients with food allergy to Wheat (46). In a study of patients with WDEIA, IgE antibodies to alpha-gliadin were demonstrated in 13 of 18. The study also demonstrated cross-reactivity between this allergen and gamma-gliadin, suggesting that treatment with a Gluten-free diet, *i.e.*, a diet excluding Wheat, Rye, and Barley, is indicated for all patients with WDEIA (35).

Tri a beta Gliadin, a beta-gliadin, was reported to be present in 60% of sera of 28 patients with food allergy to Wheat (46).

Tri a gamma Gliadin, a gamma-gliadin, was reported to be present in 55% of sera of 28 patients with food allergy to Wheat (46). In a study of 4 male Japanese patients, aged 39 to 53, with WDEIA, gamma-gliadin appeared to be a dominant allergen, causing the anaphylactic symptoms in these patients (41).

Tri a omega-2 Gliadin is an omega-gliadin. Among the allergens of the gliadin group, the omega-5 gliadin, a component of fast omega-gliadin, is a major allergen of Wheat-dependent exercise-induced anaphylaxis/asthma (WDEIA) (33-35,38,41-42,45,71). In a study to determine IgE binding against a panel of purified gluten proteins by using sera from 15 patients with WDEIA, approximately 80% of the patients reacted to fast omega-gliadin, strongly confirming that this allergen is a predominant allergen for WDEIA (33). The sera of all of these 15 patients also reacted to slow omega-gliadin, LMW, and HMW glutenin, apart from the strong reactivity to fast omega-gliadin (33). See also rTri a 19; Omega-5 Gliadin f416.

Omega-5 gliadin is also an allergen for children with an immediate-type allergy to Wheat (38). Transglutaminase-mediated cross-linking of a pepsin-trypsin-digested omega-5 gliadin was shown to cause a marked increase in IgE-binding both *in vitro* and *in vivo*. (36) Allergen-specific IgE shows fast omega-gliadin cross-reacting with gamma-gliadin and slow omega-gliadin (34,41-42). Gamma-70 and gamma-35 secalins in Rye and gamma-3 hordein in Barley cross-react with omega-5 gliadin (37). Fast gamma-gliadin is also called 1B-type omega-gliadin (72). Fast omega gliadins, which correspond to omega-5 gliadins, have also been suspected to be allergenic in bakers' asthma (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected (73). Studies have also reported various degrees of cross-reactivity among different Wheat allergens. Water/salt-soluble proteins were reported to cross-react with alpha-gliadin and total glutenins, the water/salt-soluble proteins sharing cross-reacting epitopes with water/salt-insoluble proteins. The authors suggested that the development of IgE antibodies to alpha-gliadin may in part depend on the presence of cross-reacting antibodies to water/salt-soluble Wheat allergens (2). Clear cross-reactivity was also reported between gliadin and other fractions; the authors concluded that identical epitopes are found in several different allergenic molecules of the cereal flours despite their different solubility (2).

Fast omega-gliadin is a major allergen among water/salt-insoluble proteins in the case of WDEIA in Japanese patients, and IgE against fast omega-gliadin cross-reacts to gamma-gliadin and slow omega-gliadin (34). Further studies have reported that gamma-70 and gamma-35 secalins in Rye and gamma-3 hordein in Barley cross-react with omega-5 gliadin, suggesting that Rye and Barley may elicit symptoms in patients with Wheat-dependent exercise-induced anaphylaxis. In immunoblotting, anti-omega-5 gliadin antibodies bound to 70 kDa and 32 kDa proteins in Rye and to a 34-kDa protein in Barley, but not to proteins in Oats. These proteins were identified as Rye gamma-70 secalin, Rye gamma-35 secalin and Barley gamma-3 hordein, respectively. In ELISA studies, 21/23 (91%) patients with WDEIA showed IgE antibodies to purified gamma-70 secalin, 19/23 (83%) to gamma-35 secalin and 21/23 (91%) to gamma-3 hordein. Skin prick testing gave positive reactions to gamma-70 secalin in 10/15 (67%) patients, to gamma-35 secalin in 3/15 (20%) patients and to gamma-3 hordein in 7/15 (47%) patients (37).

Considerable similarity has been reported among the major allergenic protein of maturing Rice seeds, Barley trypsin inhibitor, and Wheat alpha-amylase inhibitor (74).

Although extensive cross-reactivity can be expected among the varieties of Wheat, Einkorn wheats, particularly *T. monococcum*, are suspected to be less toxic than bread and pasta Wheats to patients with coeliac disease (75). Most lines of Einkorn wheats have been reported to lack the highly allergenic components of the alpha-amylase inhibitor family, but their flour/salt-soluble extracts show levels of IgE-binding similar to those of bread and pasta Wheats. Putative major allergens with molecular sizes from 20 to 60 kDa in Einkorn Wheats are responsible for the latter result (76).

Laboratory investigation has reported that Wheat flour allergens were immunologically partially identical to antigens of Rye flour and of common grass pollen (77-78). Further RAST inhibition experiments showed cross-reactivity between grain extracts of Wheat, Rye, Barley and Oats, suggesting that the bran layers of cereal grains are at least as allergenic as the flour (79). Cross-reactivity has been reported not only among the flours of Wheat, Rye, Barley and Oats, but also Corn and Rice, as shown by RAST inhibition tests (80). Synthetic Lol p 5 from Rye grass recognised proteins of other clinically important grass pollens, including Wheat, further indicating the presence of cross-reactivity at the level of allergenic epitope (81).

A putative class I chitinase recognised by sera from patients with Latex-fruit allergy was described in Chestnut, Cherimoya, Passion fruit, Kiwi, Papaya, Mango, Tomato, and Wheat flour extracts (47).

A lipid transfer protein, found in Spelt, was reported to be highly homologous to other LTPs from Wheat, Barley, Rice, Maize and Peach (29-30).

Clinical Experience

IgE-mediated reactions

Wheat is among the 6 most important food items accounting for hypersensitivity reactions in children. Special adverse reactions to Wheat protein include:

1. Baker's asthma (an IgE-mediated reaction to inhaled flour from Wheat and other grains)
2. Coeliac disease, a non-IgE-mediated enteropathy caused by Wheat gliadin, and
3. Wheat-dependant exercise-induced asthma or anaphylaxis.

The onset of adverse reactions may be immediate, delayed, or both immediate and delayed (17). Differences in the specific allergens, the routes of sensitisation, and the end-organ responsiveness have not been completely understood or elucidated. Wheat hypersensitivity has been reported in both occupational and non-occupational settings and may occur to Wheat or Wheat flour (7,82- 84).

Overview of food allergy to Wheat

Hypersensitivity reactions to ingested Wheat protein have been commonly reported, including by investigators performing blinded food challenges in children (17,85). In Japan, for example, Wheat is reported to be the food allergen causing the most reactions (86). Hypersensitivity reactions to ingested Wheat protein typically occur within an hour after Wheat ingestion and include gastrointestinal, respiratory and cutaneous symptoms (87). Adverse reactions typically occur within an hour after Wheat ingestion and include cutaneous, gastro-intestinal, and respiratory symptoms. Affected individuals are usually sensitised during infancy (88) and unlike in Peanut and shellfish allergy, the clinical reactivity typically resolves before adulthood.

Sensitisation to Wheat by ingestion can lead to food allergy symptoms and WDEIA, whereas sensitisation by inhalation can cause baker's asthma and rhinitis. Wheat omega-5 gliadin (Tri a 19) has been shown to be a major allergen in children with immediate allergy to ingested Wheat. Of 40 children with suspected Wheat allergy who presented with atopic dermatitis and/or gastro-intestinal and/or respiratory symptoms, after oral Wheat challenge, 19 children (48%) had immediate reactions and 8 children (20%) had delayed hypersensitivity symptoms. Sixteen (84%) of those with immediate symptoms had IgE antibodies to omega-5 gliadin. In contrast, IgE antibodies to omega-5 gliadin were not detected in any of the children with delayed or negative challenge test results. Skin prick testing with omega-5 gliadin was positive in 6 of 7 children with immediate challenge symptoms and negative in 2 children with delayed challenge symptoms (38). In a study, 60% of 28 patients with food allergy to Wheat had IgE antibodies directed against alpha- and beta-gliadins and LMW glutenin subunits, 55% of the affected group to gamma-gliadins, 48% to omega-gliadins and 26% to HMW glutenins. Further analysis also showed that 67% of patients had IgE antibodies to the albumin/globulin fraction (46).

Anaphylaxis

Wheat exposure may result in life-threatening anaphylactic reactions. (89) Minute residual Wheat protein may be responsible. A Wheat-allergic boy experienced systemic urticaria and angioedema within 40 minutes after the ingestion of 9 g of packed rice crackers which contained a trace quantity of Wheat protein, 1.50 µg/g. Three of 8 other kinds of processed rice crackers were contaminated by Wheat protein, with levels ranging from 0.26 to 1.13 µg/g. The authors concluded that approximately 13.5 µg of Wheat protein can elicit a systemic adverse reaction in highly sensitive Wheat-allergic individuals (90).

According to an analysis of a group of 580 patients in France with reactions to food, 60 presented with severe, near-fatal reactions. The foods most frequently incriminated in anaphylactic reactions were Celery (30%), crustaceans (17%), fish (13%), Peanuts (12%), Mango (6%), and Mustard (3%). Sensitisation to foods in the group tested was as follows: Wheat (39%), Peanuts (37%), Crab (34%), Celery (30%), and Soy (30%) (91).

Anaphylaxis to Wheat flour was also described in a 9-month-old child who had eaten cereal baby food. The allergens responsible were attributed to the Wheat alpha-amylase inhibitor subunits CM3 and CM16. CM2, CM3 and CM16 were found to be involved in baker's asthma (92).

Nonsteroidal anti-inflammatory drugs enhanced allergic reactions in a patient with Wheat-induced anaphylaxis (93).

Anaphylaxis has also been reported to Wheat isolates (60).

Wheat-dependent exercise-induced anaphylaxis (WDEIA)

WDEIA is a severe IgE-mediated allergic reaction provoked by the combination of Wheat or Wheat flour ingestion with intensive physical exercise during the next few hours (39,41-43,86,94-98). Typical symptoms are generalised urticaria and severe allergic reactions such a shock or hypotension (33). Wheat allergy is common in children but rare in adults, but Wheat-dependant exercise-induced anaphylaxis is common across the spectrum (99). Eighteen patients were described who had experienced recurrent episodes of generalised urticaria during exercise, 17 patients in association with collapse and 15 patients with an anaphylactic reaction. The symptoms appeared only when the patients had eaten food containing Wheat before exercise (35). WDEIA may occur to multiple food intake (100).

The threshold amount of ingested Wheat resulting in WDEIA has not yet been elucidated, but in a report of a 24-year-old Japanese woman who suffered for 2 years from attacks of urticaria, dyspnoea and syncope associated with exercise after the ingestion of Wheat, symptoms were induced following the ingestion of 64 g of bread, but not 45 g (101). Although ingestion of Wheat alone may result in WDEIA, there is a report of a 14-year-old boy who was shown to develop food-dependant exercise-induced anaphylaxis only on provocation testing with simultaneous intake of Wheat and umeboshi, but not when each food was eaten singly (102). A study reports on a 48-year-old female who developed urticaria, angioedema, dyspnoea and loss of consciousness after a restaurant meal. A second episode occurred. These reactions could be elicited in the ward only with a combination of Wheat flour, ethanol, additives and exercise (99).

Food-dependent exercised-induced cholinergic urticaria to Wheat occurring in a 24-year-old woman has been described (103).

Of the Wheat proteins, omega-5 gliadin (Tri a 19), one of the components of fast omega-gliadin, has been reported as a major allergen in WDEIA (19). Although the mechanism is not fully understood, a study reports that omega-5 gliadin-derived peptides are cross-linked by tissue transglutaminase (tTG), which causes a marked increase in IgE binding both *in vitro* and *in vivo*. Activation of tTG, during exercise, in the intestinal mucosa of patients with WDEIA could lead to the formation of large allergen complexes capable of eliciting anaphylactic reactions (36). A study suggests that, in addition to IgE

antibodies against omega-5 gliadin, IgA antibodies may be involved in the pathogenesis of WDEIA (40).

Although omega-5 gliadin is the predominant allergen in WDEIA and is a component of gluten, in a study of patients with WDEIA, some were reported to be negative in IgE antibody tests for gluten, suggesting unreliable sensitivity of the test for the diagnosis of WDEIA; the findings implied that the measurement of IgE antibodies to gluten is not always satisfactory for the screening as well as diagnosis of WDEIA (33).

Pre-treatment with sodium bicarbonate appears to inhibit the reappearance of anaphylactic symptoms following Wheat ingestion and exercise provocation (104).

Although this is not an instance of WDEIA, a male athlete is described who suffered respiratory arrest following a run through a Wheat field, a run which had caused Wheat pollen to be released. He had multiple wheals on both legs and complained of severe breathlessness before collapsing. The authors suggest that it was possible that the symptoms were triggered either by the running itself, inhalation of allergens other than Wheat pollen, skin abrasions caused by contact with Wheat stalks, or a combination of these factors (105).

Atopic Eczema

Wheat allergy may result in or exacerbate atopic eczema (85,106).

In 34 children with atopic dermatitis, 33 were SPT-positive with Wheat, and 18 with Oats. Positive IgE antibody tests to Wheat and Oats could be detected in 32 and 30 samples respectively. SPT with Rice, Corn, Millet or Buckwheat was positive in 16/34 patients (10). The strong association between positive oral Wheat challenge and positive skin reactivity with ethanol-soluble gliadin suggests that gliadin is an important allergen in Wheat-allergic children with AD (107).

SPT with a NaCl Wheat suspension and ethanol-soluble Wheat gliadin was performed on 18 Wheat-challenge-positive or -negative children with AD, 6 adult AD patients with suspected cereal allergy, and 1 adult with Wheat-dependent exercise-induced urticaria/anaphylaxis. It was reported that 13 of the AD children were Wheat-challenge-positive, that 11 were positive for gliadin SPT, and that all had elevated gluten-specific IgE. Those who were challenge-negative were negative with both gliadin SPT and gluten-specific IgE. Four of the adult patients responded to a cereal-free diet, although only 2 of them appeared to be positive with gliadin SPT and gluten-specific IgE determinations (107).

Ocular-type atopic dermatitis belongs to the most severe end of the spectrum of AD, and IgE antibodies to Rice and Wheat were significantly higher in this form of AD. The authors suggest that food antigens may contribute to severe AD, resulting in ocular complications (108).

Allergic contact dermatitis from hydrolyzed Wheat protein in cosmetic cream has been reported (109).

Other cutaneous reactions

Chronic urticaria to ingestion of Wheat has been reported (110).

Other IgE-mediated food reactions

A significant association has been reported between recurrent serous otitis media and food allergy in 81 of 104 patients. An elimination diet resulted in a significant amelioration of the disease in 86% of the patients, and a challenge diet provoked recurrence of symptoms in 94%. The highest frequency was seen with Cow's milk, Wheat, egg, Peanut, Soy and Maize, and <10% frequency was seen with Orange, Tomato, Chicken and Apple (111).

Allergy to Wheat may also result in eosinophilic esophagitis (112).

Wheat may be a “hidden allergen” (113).

Baker's asthma

Baker's asthma is a frequent allergy in the baking industry. In Germany, approximately 1,800 bakers annually claim compensation for baker's asthma (114). The prevalence of asthma among bakers has been shown to be around 10%, and the prevalence of cereal allergy 15-25% (115-116). Of those bakers

who have cereal allergy, up to 35% experience asthma (78). In Japan in recent years, the number of patients suffering from baker's asthma caused by bread Wheat has been increasing, and includes not only people engaged in food industries, but also those who live near a factory producing Wheat flour products (117).

Several protein components of salt extracts of Wheat flour weighing from 10 to 100 kDa have been identified as major IgE-binding proteins in occupational asthma (118). Allergen-specific IgE antibodies to a number of flour components have been demonstrated in allergic bakers' sera with the strongest reactivities occurring to water-soluble Wheat albumins and globulins, the former being shown in inhibition studies to be more reactive than the latter (12-13,119). However, further analyses have demonstrated that major IgE-binding proteins are found in other fractions (gliadin and glutenin) as well. (13) Therefore, it is no surprise that serum IgE antibodies from different allergic bakers have markedly different specificities and bind to numerous Wheat proteins (119). The major allergens are reported to be 15, 17, and 47 kDa allergens of Wheat (6) the 15 kDa Wheat allergen belonging to the alpha-amylase/ trypsin inhibitor family (5,82). In ingested cereal allergy and atopic dermatitis, the IgE responses have appeared more poly-specific, being directed against over 30 individual bands of Wheat, Rye and Barley in IgE immunoblotting (10,14). Wheat flour peroxidase has also been reported to be a prominent allergen associated with baker's asthma (70). Several water-soluble Wheat molecules exhibit identical epitopes (120). Wheat flour proteins are allergens for 60% to 70% of bakers with workplace-related respiratory symptoms. Nevertheless, a great inter-individual variation of IgE-binding patterns of Wheat flour proteins occurs in baker's asthma (18).

Although baker's asthma (121-123) is an occupational hypersensitivity disease primarily caused by the inhalation of flour proteins, which are mainly derived from Wheat, the disease may also be caused by flour proteins from Rye, Barley or Soya (83-84). However, the allergens involved in baker's asthma are not limited to cereal allergens. Exposure possibilities in a bakery range from mould and mite contaminants to several additive agents used in the baking. For example, in a study of bakers with workplace-related respiratory symptoms, sensitisation to Wheat flour was demonstrated in 64%, to Rye flour in 52%, to Soy flour in 25%, and to alpha-amylase in 21% (114).

Cereal alpha- and beta-amylases may be more important allergens than fungal alpha-amylase. IgE antibody determination analysis showed that 29 of 30 subjects with inhalant-induced cereal allergy had IgE antibodies to cereal amylases, but that only 16 were positive to fungal alpha-amylase; RAST inhibition showed little cross-reactivity between cereal and fungal alpha-amylases (124).

Other occupational conditions

Occupational exposure to Wheat or Wheat dust may result in a number of other allergic conditions besides baker's asthma, and may involve animal workers, bakers and bakery, food industry, and mill workers.

In bakers, rhinitis, itching, skin eruptions, ocular symptoms (including tearing, itching and conjunctival injection) and respiratory symptoms (including cough and sputum production) have been reported. In a study, 44.4% of affected individuals were shown to have Wheat flour-specific IgE (125).

Occupational protein contact dermatitis has been described (126).

Cereal flours are used in the wood industry to improve the quality of the glues necessary to produce veneer panels. Three individuals were found to be allergic to cereal alpha-amylase inhibitors found in Wheat, which are important occupational allergens responsible for baker's asthma (127).

Asthma can be related to exposure to cereal flour contained in animal formula feeds (128).

Other reactions

Non-IgE immune reactions to gluten may result in coeliac disease. Even low levels of immuno-reactive gliadin (0.75 mg/100 g) found in Wheat starch may affect these individuals. In one study, the majority of the patients with coeliac disease (11 of 17) who had never consumed Wheat starch previously developed symptoms, which resolved within weeks of discontinuing the offending product (129).

In an Indian study, 39 children suffering from Wheat harvest-period respiratory allergy, along with randomly selected controls, were investigated for allergy symptoms. Of the allergic children, 81% had skin reactivity to antigen of Wheat threshing dust, 30% to fungal antigens, 14% to Wheat dust antigens and none to Wheat plant antigens (130).

Various Wheat and Soy protein sources, including the Soy protein isolates used to make infant formulas, may be related to juvenile or insulin-dependent diabetes mellitus (131-132).

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Phaseolus vulgaris

Family:	*Fabaceae* (*Leguminosae*)
Common names:	White bean, Cannellini bean, Marrow bean, Great northern bean, White kidney bean, Haricot bean
Source material:	Dried beans
Synonym:	*P. vulgaris var. humilis*
See also:	Red kidney bean f287 and Green bean f315

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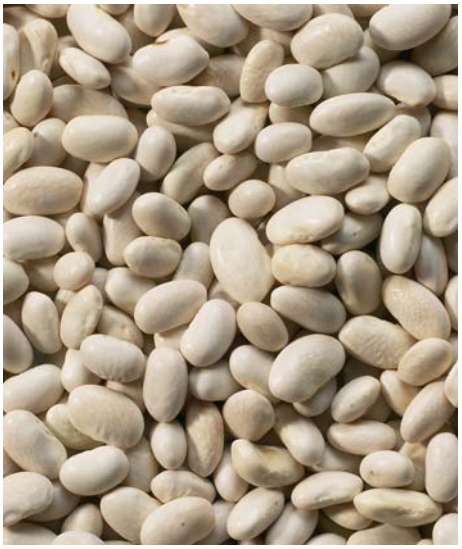

Allergen Exposure

Geographical distribution

White bean (the beans actually range in colour from pale green to creamy white) is a term given to varieties of beans that have light-coloured seeds. They are less robust in flavour than the Green bean and Red kidney bean, but in some countries they are a staple food. There are several varieties of White beans, each tending to be used in different dishes. For example, White beans may be used as "Haricot beans" in stews, or as canned baked beans.

Environment

White beans are traditionally eaten alone, without the pods. They are usually available only canned, dried or (occasionally) frozen. They are baked with sauces, or added to soups, stews and baked dishes. The seed may be sprouted and used in salads or cooked. White beans are an excellent source of iron and folate and a good source of magnesium, phosphorus, potassium, and copper.

The green or dried mature pods, or the seeds alone, are reported to have diuretic, hypoglycaemic and hypotensive actions. The seeds or the whole plant may be used as a homeopathic remedy for a variety of diseases. Ground into flour, the seeds are used externally in the treatment of ulcers.

Allergens

No allergens from this plant have yet been characterised.

An alpha-amylase inhibitor has been isolated (1). The allergenicity of this protein has not been determined yet.

Phaseolus vulgaris contains a chitinase of unknown allergenicity (2).

Potential cross-reactivity

An extensive cross-reactivity among the different individual species of the genus could be expected but in fact is not seen frequently (3).

Legumes have structurally homologous proteins, but they are not all equally allergenic, making it difficult to distinguish *in vitro* and *in vivo* cross-reactivity. In SPT serum IgE antibody tests, most patients are shown to be sensitised to more than 1 species, but this may be clinically irrelevant. For example, in an *in vitro* study, the specific IgE binding by protein extracts of 11 food legumes was examined by IgE antibody determination and RAST inhibition. Cross-allergenicity was demonstrated to be most marked between the extracts of Peanut, Garden pea, Chick pea, and Soybean (4-5), and between Pea and Soybean (6). However, clinical studies have found that there is little cross-reactivity between members of the legume family (7-9).

In a recent Spanish study, a high degree of cross-reactivity was demonstrated by inhibition studies among Lentil, Chick pea, Pea and Peanut. The majority of the study group had had symptoms with more than 1 legume (median 3 legumes). Thirty-nine patients were challenged (open or simple blind) with 2 or more legumes and 32 (82%) reacted to 2 or more legumes: 43.5% to 3, 25.6% to 2, 13% to 4 legumes. Seventy-three per cent of the patients challenged with Lentil and Pea had positive challenges to both, 69.4% to Lentil and Chick pea, 60% to Chick pea, and 64.3% to Lentil, Chick pea and Pea simultaneously. However, White bean, Green bean and Soy were generally well tolerated by children allergic to other legumes. The authors argued that, unlike in the Anglo-Saxon population, this phenomenon implies clinical sensitisation for many Spanish children (10).

The Peanut vicilin storage protein shares significant sequence homology with the vicilin storage proteins of other legumes, *e.g.*, Soybean, Pea, and Common bean (11). This does not necessarily indicate clinical cross-reactivity but would explain why IgE antibodies to other legumes may be found in serum.

A study investigated the *in vitro* cross-reactivity of allergens from Mesquite tree pollen (Honey locust tree; *Prosopis juliflora*) and Lima bean (*Phaseolus limensis/ Phaseolus lunatus*). Of 110 patients with asthma, rhinitis or both, as evaluated by intradermal test, 20 were highly positive to Mesquite pollen extract. Of these, 12 patients showed elevated IgE antibody level to Mesquite pollen extract alone, and 4 to both Lima bean and pollen extract. Lima bean extract could inhibit IgE binding to Mesquite in a dose-dependent manner. Also, humoral and cellular cross-reactivity was demonstrated (12). Although cross-reactivity was not investigated between Mesquite and White bean *per se*, cross-reactivity may exist between pollen from this tree and other species of *Phaseolus*.

Clinical Experience

IgE-mediated reactions

White bean may uncommonly induce symptoms of food allergy in sensitised individuals.

A study reports on a 33-year-old woman who developed tongue swelling and burning and mouth itching minutes after eating baked Beans. Similar symptoms occurred a day after ingesting Pea soup, on another occasion within 15 minutes of eating a Bean burrito, and again 20 minutes after eating chilli containing Kidney and Pinto beans. In this last instance, she also developed chest tightness, wheezing, generalised erythema, urticaria, abdominal pain, a feeling of impending doom and light-headedness. SPT was positive to Red kidney and White bean, but negative to Pea, Green and Lima bean. IgE antibodies were found to Red kidney, Pinto and White bean, and to Chick pea, Pea and Black-eyed pea (13).

A 7-year-old boy was described who developed angioedema associated with inhalation of vapours from cooked White bean. SPT evaluation using the prick-to-prick method was positive for White bean. IgE antibody determination was positive for White bean and Green bean. The patient also developed angioedema after ingesting cooked White bean (14).

Other reactions

The root is dangerously narcotic. Large quantities of the raw mature seed may be poisonous. Flatulence is also a hazard.

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Mixes

These tests consist of a mixture of different allergens, related or unrelated. For specific information about the included allergens consult the separate descriptions.

fx1

Peanut (f13)	page 132
Hazel nut (f17)	page 81
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Milk (f2)[1]	
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Refers to other books in the serie Allergy – Which Allergens?

[1]Food of Animal Origin
[2]Food of Plant Origin – Fruits & Vegetables
[3]Food of Plant Origin – Additives, Spices & Miscellaneous

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Mixes

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fx28

Sesame seed (f10)	page 192
Shrimp (f24)[1]	
Beef (f27)[1]	
Kiwi (f84)[2]	

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