meat technology
Founder and publisher: Institute of Meat Hygiene and Technology, Belgrade

UDK: 616-056.3:663/664
ID: 69369353
https://doi.org/10.18485/meattech.2022.63.1.2

Review paper

Food allergens — food safety hazard

Jovanka Popov Raljić[1], Milica Aleksić[2], Vesna Janković[3]

A b s t r a c t: Food allergens have appeared in the last two decades as a concealed form of threat which significantly endangers public health, and their labelling on food products, drinks, and non pre-packed gastro-products is clearly defined by legal regulations. Food allergy is a life-threatening chronic condition that substantially impairs quality of life. Food allergies constitute a significant public health problem that affects children and adults and is a considerable burden on health, medical systems and emerging economies. Appropriately managing food allergies has become an issue for the food industry because of the rising number of individuals with food allergies.

Keywords: *food allergy, food allergens, big eight.*

Introduction

Food allergy is a life-threatening chronic illness that severely limits the individual's quality of life. These allergies are a significant part of public health policy. Children and adults are afflicted, and the cost to health, medical systems, and expanding economies is enormous (*Greenhawt*, 2016). Food allergy is described as a negative health consequence caused by a specific immune-mediated reaction that happens consistently after eating a specific food (*Boyce et al.*, 2010; *Wang and Sampson*, 2011), and food-specific IgE antibodies, cellular processes, or both can be involved (*Muraro et al.*, 2014).

Food allergy is defined by the European Academy of Allergology and Clinical Immunology (EAACI) as a subclass of adverse reactions in which the immune system plays a role. Food allergies are categorised as IgE-mediated, non-IgE-mediated, or

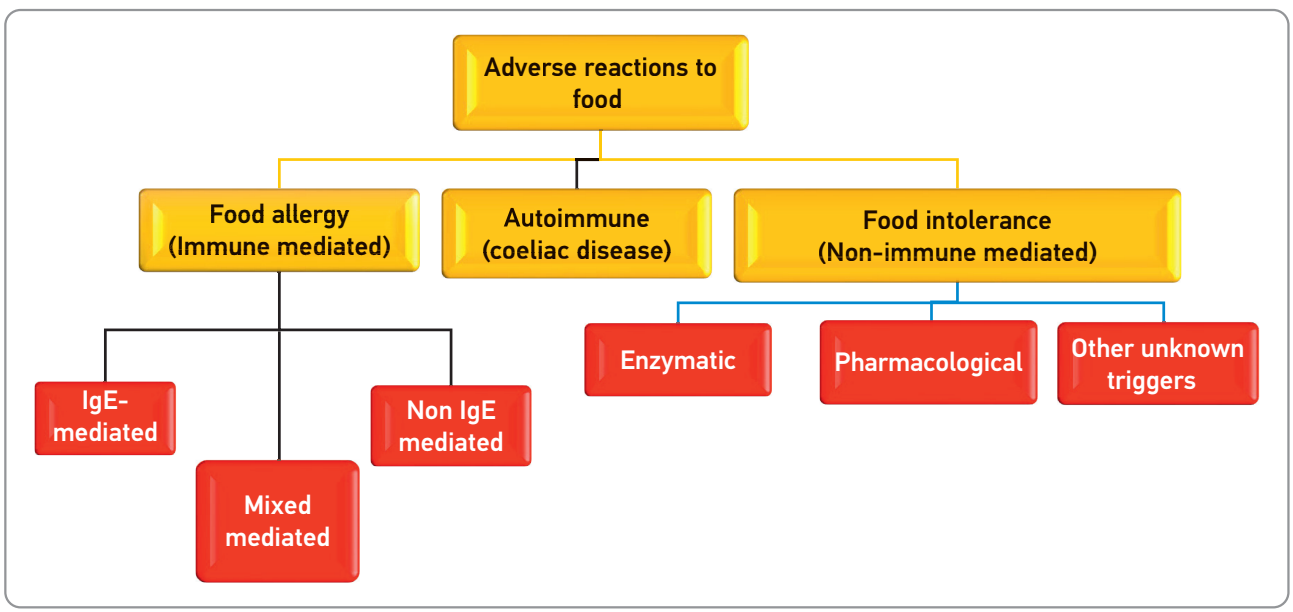

Figure 1. Classification of adverse reactions to food (*Johansson et al.*, 2001; *EFSA*, 2014)

[1] *Singidunum University, Faculty of Tourism and Hotel Management, Danijelova 32, 11000 Belgrade, Serbia;*
[2] *University of Business Studies, Faculty of Tourism and Hotel Management, Jovana Dučića 23 a, 78000 Banja Luka, Republika Srpska, Bosnia and Herzegovina;*
[3] *Institute of Meat Hygiene and Technology, Kaćanskog 13, 11000 Belgrade, Serbia.*

Corresponding author: Vesna Janković, vesna.jankovic@inmes.rs

mixed IgE and non-IgE-mediated reactions based on the mechanism of occurrence (*Sampson* 2004; 2007; *Wang and Sampson*, 2011).

According to the European Food Safety Authority (*EFSA*, 2014), adverse food reactions are divided into classes based on the pathogenic mechanism (Figure 1). They include immunologically mediated reactions, which are mediated either by IgE antibodies, by cells (non-IgE-mediated) or both (mixed), and non-immunological responses (food intolerance), which are dependent on enzyme deficiencies or pharmacological reactions or, in the majority of cases, arise by unknown mechanisms (*Vickery et al*., 2011; *Muraro et al*., 2014; *Waserman and Watson*, 2018).

Food-induced immune-mediated adverse reactions show as clinical signs and symptoms of varying intensity and duration, affecting many organs and systems. Food-induced anaphylactic responses are mediated by IgE and can occur at any age (*Yue et al.*, 2018). Protein-induced enterocolitis and eosinophilic oesophagitis are two illnesses caused by non-IgE-mediated food allergies (*EFSA*, 2014; *Connors et al.,* 2018).

Food allergen epidemiology

In developed countries, the prevalence of food allergies is unknown. The major causes for this uncertainty are the scarcity of studies available for specific geographic areas and the use of diverse procedures among studies to derive prevalence data (*Huiwen and Leung*, 2018).

Food allergy prevalences and patterns are significantly diverse in different parts of the world (the second wave of the allergy epidemic). A complex combination of genetic, epigenetic, and environmental variables could create differences in food allergy epidemiology (migration, climate and infant feeding practices). When considering data from Europe, based on a meta-analysis of published food challenge data, cow's milk, tree nuts, soy, hen's egg, peanut, wheat, fish and shellfish were the most common elicitors of food allergy in Europe with an estimated accumulated prevalence of 2.1% (1.2 to 3.3%) of the population, while in the United States, and Australia/New Zealand, the prevalence of food allergy has been estimated to be around 3% (*Prescott and Allen*, 2011; *Holzhauser et al*., 2020). However, there was a lot of variation in the research utilized to determine the prevalence of food allergies. There is inadequate objective evidence to draw any conclusions on time patterns in the prevalence of food allergies in Europe. Egg, peanut, cow's milk, seafood and other nuts cause over 75% of allergy reactions in youngsters. Adults are allergic to around half of the fruits and vegetables in the Apiaceae family, as well as numerous nuts and peanuts (*EFSA*, 2014).

Food allergy prevalence varies by region according to environmental (e.g. pollen exposure or food habits) and individual factors. Individual characteristics considered crucial in the development of food allergy include sex, age, family history of atopy and the presence of other allergic illnesses. Due to variances in genetic background, exposure to offending foods, and eating habits, extrapolating prevalence data on specific food allergies from a single European country to the entire European population has limited accuracy.

There is currently no available treatment for food allergies. To avoid an allergic reaction, which can be severe and life-threatening, strict allergen avoidance remains the most effective allergy management strategy (*Muraro et al*., 2014). Identification of the relevant dietary allergen is essential for successful allergy avoidance. The European Union (EU) food information regulation was created to allow consumers to easily identify relevant allergies (*Regulation EU* 1169/2011, 2011), and in Serbia, the *Rulebook on declaration, labeling and advertising of food* (*Official Gazette of RS*, No. 19/2017, 16/2018, 17/2020 and 118/2020), *Rulebook on health correctness of diet foods* (Official Gazette of RS, No. 45/2010, 27/2011, 50/2012, 21/2015, 75/2015, 7/2017 and 103/2018 — other rulebook) requires the mandatory labelling of 14 allergenic foods or food groups, including the above-mentioned allergens, when they are used as ingredients in manufactured foods.

Food allergens

The EU food information regulation (*EU*, 2011) does not apply to non-ingredient allergenic components that may arise via cross-contact, such as during manufacturing or packing. Food makers can use voluntary precautionary allergen labelling (PAL) to educate and protect allergy sufferers in the event of the presence of unintended allergens (*Muraro et al*., 2014a). Unfortunately, mislabelling and sporadic use of PAL that is not based on quantitative allergy risk assessment might result in a mismatch between labelling and allergen presence (*Allen et al*., 2014; *Crotty and Taylor*, 2010; *Remington et al*., 2015), and as a result, allergic consumers face considerable risks, and their product options are limited

(*Holzhauser et al*., 2020). In Serbia, the Ordinance on declaring, labeling and advertising of food (Official Gazette of RS, No. 19/2017, 16/2018, 17/2020 and 118/2020) and the Ordinance on the health safety of dietary foods (Official Gazette of RS, No. 45/2010, 27/2011, 50/2012, 21/2015, 75/2015, 7/2017 and 103/2018) provide allergen legislation considering 14 food ingredients that can cause allergic reactions or intolerance, method of declaration, recommended method for detection of gluten in foods, etc. In this paper, data for the eight major allergenic foods will be presented (the big eight).

Cereals containing gluten and cereal products

Wheat flour is used as a raw material for bakery items (bread, pastries, pizza), pasta (noodles, pasta, spaghetti), some confectionery (cakes, biscuits, gingerbread), and ready meals (cream soups, sauces etc.) (*Psodorov*, 2014; *Popov-Raljić*, 2016).

In order to generate a functional product, flour formed by grinding pseudocereals such as amaranth, buckwheat, quinoa, sorghum or other plant material is increasingly utilized in addition to wheatflour, as are combinations of different types of flours from small grains such as oats, barley, rye or corn (*Alvarez-Jubete et al.,* 2010; *Sakač et al.,* 2011).

Table 1 illustrates gluten-containing cereals (wheat, rye, oats, barley, spelt, kamut, and cross-bred types) and their reference doses in relation to some of the most often consumed foods (*Popov-Raljić et al.,* 2017). The majority of gluten-free items on the market are made with starch; however, gluten-free food makers frequently employ whole grains like corn, corn, amaranth and quinoa, which are high in fibre, iron and vitamin B (*Lorenzo et al.,* 2018).

Allergic reactions to wheat and other cereals are most frequent in infants, and they normally pass during the first few years of life. IgE-mediated cereal allergy symptoms range from minor local skin or gastrointestinal reactions to more acute, often life-threatening anaphylactic episodes. Bakers' asthma (occupational exposure to grain flour dust) and, less commonly, IgE-mediated allergy

Table 1. Cereals containing gluten and cereal products — *Popov-Raljić et al.* (2017), *The German Federal Institute for Risk Assessment (BfR), https://www.bfr.bund.de/*(2020)

Allergen and reference dose (mg)	Prevalence and severity	Some derivatives (additives) and allergen-containing foods that can cause allergic responses
Wheat, wheatberries, rye, barley, spelt, kamut®, triticale, durum wheat or semolina, club wheat, emmer, einkorn, farro, and varieties created by their crossing, except glucose syrup based on wheat and dextrose, maltodextrin based on wheat, glucose syrups based on barley, and cereal distillates or ethyl alcohol of agricultural origin for the manufacturing of strong alcohol beverages obtained from cereals.  Reference dose = 0.7 mg protein **(VITAL 3.0, 2019, ED_{01})**	Celiac disease or gluten intolerance. Cereal allergens can cross-react with pollen allergens.	✓ Flour ✓ Starch ✓ Bran ✓ Rusks ✓ Bread, bread ✓ Grits ✓ Couscous ✓ Hydrolysed vegetable protein (if derived from wheat)

Table 2. Allergenic proteins (*Fagopyrum esculentum* — Common buckwheat, *Fagopyrum tataricum* – Tartarian buckwheat, *Triticum aestivum* — wheat, *Triticum turgidum ssp durum* — Durum wheat) (WHO/IUIS — Allergen Nomenclature Sub-committee, *www. allergen. org-allergen nomenclature*)

Fagopyrum esculentum	**Allergen exposure route**	
Allergen	Food	
Fag e	Fag e 2–5	
Fagopyrum tataricum		
Allergen	Food	
Fag t	Fag t2, Fag t6	
Triticum aestivum	Food	Airway
Allergen		
Tri a	Tri a 12, 14, 17- 21, 25–28, 36, 37, 41–45	Tri a15, 29–35, 39, 40
Triticum turgidum ssp. durum	Food	
Tri tu	Tri tu 14	

related to exercise, known as wheat-dependent exercise-induced anaphylaxis, are examples of wheat allergy. Rice is generally tolerated by people sensitive to wheat-related crops (barley, oats, and rye). Rice allergies are uncommon in Europe and America, but they may be more common in Asia. Gluten-related illnesses have gained increased epidemiological significance, with an estimated global frequency of roughly 5%. Gluten-related illnesses include celiac disease, wheat allergy, and non-celiac gluten sensitivity. Gluten-derived peptides cause a T-cell mediated autoimmune reaction in celiac disease (*Rubio-Tapia and Murray*, 2010). The classical enteropathy and malabsorption syndrome are caused by an autoimmune inflammatory cascade in the small bowel.

Celiac disease is the most well-known gluten-related condition to date: the genetic propensity of patients, the relationship with other autoimmune disorders and celiac disease's consequences have all been widely researched. Wheat allergy is an allergic reaction to proteins found in wheat and similar cereals, with varying clinical manifestations depending on the route of exposure. In this condition, Immunoglobulin E (IgE) antibodies mediate the inflammatory response to a variety of allergenic proteins (alpha-amylase/trypsin inhibitor, non-specific lipid transfer protein (nsLTP), gliadins, and HMW glutenins) (*Ludvigsson et al.*, 2013). Non-celiac gluten sensitivity is a third form of clinical reaction to gluten consumption. In the absence of celiac disease or wheat allergy, patients with non-celiac gluten sensitivity often have a wide spectrum of intestinal and extraintestinal symptoms quickly after consuming gluten-containing foods (wheat allergy) (*Catassi et al*. (2013); *Elli et al.,* (2015). Many allergenic proteins are involved in wheat allergy and the latest updated version of the WHO/IUIS Allergen Nomenclature Database describes many different well-classified wheat allergens (Table 2).

Eggs and egg products

Eggs and egg components/ingredients are frequently widely used in a variety of culinary products, including bakery and confectionery, gourmet (soups, sauces, dressings) and meat products. According to the USDA, the edible portion of the egg is made up of 63% egg white and 27.5% yolk, while 9.5% is egg shell, including the shell membrane. Egg is one of the most common allergenic foods, with an allergy prevalence of 1.8 to 2% in children under the age of five (*Lee*, 2017, *Loh and Tang*, 2018). Table 3 shows general allergy information for eggs and egg products.

Egg white contains the majority of the proteins linked to egg hypersensitivity (*Réhault-Godbert et al.,* 2019). According to *Dumont and Delahaut* (2010), both egg white and egg yolk contain clinically significant allergic egg proteins. Table 4 shows the molecular and biological properties of the identified egg allergens.

Table 3. Eggs and egg products — *Popov-Raljić et al.* (2017), *The German Federal Institute for Risk Assessment (BfR), https://www.bfr.bund.de/*(2020)

Allergen and reference dose (mg)	Prevalence and severity	Some derivatives (additives) and allergen-containing foods that can cause allergic responses
 Reference dose = 0.2 mg protein **(VITAL 3.0, 2019, ED_{01})**	Egg allergy is prevalent in youngsters, but by the age of three, more than half of them have outgrown it. Individuals may get anaphylactic crises.	✓ Powdered eggs, dried eggs or pasteurized eggs ✓ Albumin ✓ Egg glaze ✓ Mayonnaise ✓ Note: lysozyme (produced from egg albumin), which is used in refining wines, has a low risk of producing responses. However, when lysozyme is utilized for other purposes (for example, as a cheese preservative), it might have negative consequences health consequences (Schneider and Pischetsrieder, 2013)

Table 4. Molecular and biological properties of identified egg allergens *Dumont and Delahaut* (2010); *Sakai and Teshima* (2015)

EGG WHITE PROTEINS	
Ovomucoid (Gal d 1)	Inhibitor of trypsin activity Antimicrobial properties Activation of the immune system Antioxidant properties Bacteriolytic activity Antiviral activity
Ovoalbumin (Gal d 2)	
Ovotransferrin (Gal d 3)	
Lysozyme C (Gal d 4)	
EGG YOLK PROTEINS	
Serum albumin — α-livetin (Gal d5)	Inhibitor of trypsin activity Antimicrobial properties Activation of the immune system Antioxidant properties Bacteriolytic activity Antiviral activity
YGP42 (Gal d6)	
Myosin light chain 1f (Gal d7)	
α-parvalbumin (Gal d8)	
ß-enolase (Gal d9)	
Aldolase (Gal d10)	
OTHER EGG YOLK ALLERGENS These minor allergens have not been designated by the WHO/IUIS Allergen Nomenclature Sub-Committee.	
Phosvitin	This is a highly phosphorylated molecule with a high capacity for cation chelation. More than 90% of the iron in an egg is bonded to phosvitin in the yolk, according to estimates. Phosvitin has antibacterial and antioxidant properties as a result of this characteristic (*Sakai and Teshima*, 2015)
Apovitellin	The other egg yolk allergens are apovitellenin-containing lipoproteins. Apovitellenins I (Gal d Apo I) and VI (Gal d Apo VI) have been reported to show IgE-binding activity (*Sakai and Teshima*, 2015)

Table 5. Clinical symptoms associated with egg allergy — *Lack,* (2008)

Presentation	Population	Clinical Manifestation	Natural History	Egg Component	Major Allergens
Egg-white allergy	Atopy and eczema patients, in particular, are young children.	After intake, contact urticaria and systemic type 1 hypersensitivity symptoms occur.	Resolves by 7 years of age	Egg white	Ovomucoid, ovalbumin
Bird-egg syndrome*	Adults who have been exposed to birds, primarily women	Type 1 hypersensitivity symptoms after consuming egg yolks; respiratory problems following exposure to bird feathers	Persistent	Egg yolk	α-livetin (chicken serum albumin), cross-reactivity with bird feathers
Occupational egg allergy ("egg-egg" syndrome)	Adults working in the food and confectionery industries	Variable type 1 hypersensitivity symptoms (usually minor) after consuming egg white; respiratory symptoms following exposure to aerosolized egg white	Persistent	Egg white	Ovalbumin, ovomucoid, conalbumin, lysozyme

a * Oral symptoms have been reported with hen's eggs, although respiratory problems have been reported with exposure to a variety of birds

Eggs frequently cause food allergy with symptoms from a slight rash to anaphylaxis. The prevalence is expected to range from 0.2% to 7% (*Rona et al.,* 2007; *Lee*, 2017). Due to differences in patient sensitivity and the specificity of the allergen, the amount of food allergen required to provoke an allergic reaction is rarely known with any accuracy. *Taylor et al*. (2002) consider that cumulative doses that cause allergies range from 0.13 mg of raw whole egg to 200 mg of dry protein from whole egg.

The egg contains many biologically active components (*Réhault-Godbert* et al., 2019). Because egg components have many purposes (e.g., lysozyme serves as a preservative, lecithin serves as an emulsifier, and provitamin A serves as a colorant), allergens can be found in any of these food technology products if they are egg-based or egg-derived (*Audicana Berasategui et al.,* 2011).

Egg allergy is most common in children under the age of two (*Boyano-Martínez et al.,* 2002), and according to the same author, 66% of children with allergies outgrow their egg allergy after the fifth year (*Savage et al*., 2007). According to (*Caubet and Wang*, 2011) one study, children become largely immune to egg allergy at a later age (6 years old), with 37% at 10 years old and 68% at 16 years old recovering from their childhood allergy. However, over half of their 12-year-old patients were unable to consume concentrated eggs. The fact that the ratio decreases with age suggests that by the time they reach school age, newborns and toddlers have developed resistance and tolerance to eggs.

Milk and milk products

Milk is considered a complete food since it contains essential proteins, minerals, lipids and carbohydrates for human health (*Pereira et al.*, 2012). Milk includes high-quality proteins, fats, vitamins and minerals (such as potassium, phosphorus and calcium), but despite its nutritional benefits and widespread recommendations, milk consumption in Western countries is rapidly declining (*Lucarini,* 2017; *Chalupa-Krebzdak et al*., 2018; *Silva et al*., 2020). Cow's milk allergy is a common diagnosis in babies and children, and it usually disappears by the age of six. It manifests as an allergic reaction, which is the immune system's reaction to a specific milk protein. (*Edwards and Younus*, 2021).

Table 6 presents the basic characteristics, distribution and individual food/gastronomic products in which milk and dairy products can be found.

According to a survey of the literature conducted by the University of Portsmouth, forty reports on allergic reactions to milk and cow's milk products were published between 1982 and 2012. By far the most common food allergy is milk allergy (*EFSA*, 2014) which can be classified according to IgE and non-IgE mediated symptoms (*University of Portsmouth*, 2013).

Table 6. Milk and milk products — *Popov-Raljić et al.* (2017)
The German Federal Institute for Risk Assessment (BfR), https://www.bfr.bund.de/(2020)

Allergen and reference dose (mg)	Prevalence and severity	Some derivatives (additives) and allergen-containing foods that can cause allergic responses
Milk and milk products including lactose Exceptions are: whey when it is used to make distillates or agricultural ethyl alcohol for strong alcoholic and alcoholic beverages; lactitol.  Reference dose = 0.2 mg protein **(VITAL 3.0, 2019, ED_{01})**	Cow's milk allergy is the most prevalent allergy in young children, affecting 2–7% of infants under the age of one year. By the age of three, around 87% of children have outgrown their allergy. Cow's milk has a high level of cross-reactivity with the milk of other mammals like sheep, goats, and buffalo.	✓ Whey ✓ Casein ✓ Milk powder ✓ Lactose ✓ Butter, cheese, creams, yogurt, butter

Lactose is ingested and hydrolysed by lactase, an enzyme found in the microvillus membrane of enterocytes, into glucose and galactose, which are then absorbed. Undigested lactose can cause lactose intolerance symptoms if lactase activity is insufficient or absent. Subjects with galactosaemia, an inherited abnormality of galactose metabolism, also do not "tolerate" lactose, although their symptoms are more severe and differ significantly from those of lactose-intolerant subjects. Lactase activity can be stable, low, or absent due to a change (in newborns) or a drop (in adults) in lactase gene expression (primary lactase deficiency). Secondary lactase insufficiency can be caused by intestinal disease processes that destroy the epithelium of the small intestine. This condition is reversible once the underlying sickness is treated. Lactase-nonpersistence is a genetically determined and normal developmental phenomenon characterized by the down-regulation of lactase activity that occurs soon after weaning in most ethnic groups. Lactose intolerance affects people of all ages due to a deficiency in the enzyme lactase, which results in poor lactose digestion and, as a result, symptoms such as bloating, abdominal pain, and diarrhoea after ingesting milk and dairy products (*Silva et al.,* 2020). Allergenic cow's milk proteins are listed in Table 7.

Table 7. Allergenic proteins in cow's milk (*Bos domesticus*) — *www. allergen. org-allergen nomenclature*

Allergen	Biochemical name
Whey protein	
Bos d2	Lipocalin
Bos d3	S100 calcium-binding protein A7
Bos d4	α-lactalbumin
Bos d5	ß-lactoglobulin
Bos d6	Serum albumin
Bos d7	Immunoglobulin
Caseins	
Bos d8	Caseins
Bos d9	αS1-casein
Bos d10	αS2-casein
Bos d11	ß-casein
Bos d12	κ-casein
Bos d13	Myosin light chain

Many proteins in cow's milk are antigenic and capable of eliciting immunological responses, and sensitivity to diverse cow's milk proteins has been found to be widespread. The most abundant proteins in cow's milk, especially lactoglobulins, caseins, and α-lactalbumin (ALA), are the major allergens, according to studies conducted on large populations of allergic patients; however, proteins present in low quantities, such as bovine serum albumin, lactoferrin and immunoglobulins, have also proved to be important in inducing milk allergies.

Fish, crustaceans, molluscs and their products

Seafood is crucial for human nutrition, health, and economics, yet it can cause major IgE antibody-mediated adverse responses in vulnerable individuals. Fish (cod, salmon and tuna), shellfish (shrimp, crab and lobster), and molluscs (squid, shellfish and snails) are all examples of seafood. Seafood can induce severe acute hypersensitivity reactions, including deadly anaphylaxis (*Sharp and Lopata*, 2014). There are about 20,000 edible fish species, although the most regularly consumed belong to only a few groups (*Actinopterygii*). People who are allergic to fish are generally allergic to a variety of species, and therefore, they should avoid eating all fish.

Adverse reactions to seafood can be immune, such as IgE allergy mediated by the antibody for which the trigger is consumed, or non-immunological, such as poisons or pathogenic elements (*Freidl et al.,* 2017). Fish allergy affects 0.3% of the world's population, while shellfish allergy affects 0.6% (*Sicherer,* 2011), but can reach up to 8% among fish processing workers (*Sharp and Lopata*, 2014). In a survey of 17,280 adults aged 20 to 44 in countries that defined allergy or intolerance to different types of food, and based on reports that food "almost always" causes "illness or discomfort", 2.8% of respondents reported shrimp as a problem, 2.3% oysters, and 2.2% stated they were allergic or intolerant to fish (*Woods et al.,* 2001).

Parvalbumin, the most common fish allergen, as well as a few lesser-known allergens, were studied. Parvalbumins are classified as one of two isoform lineages and both are commonly found in fish (*Sharp and Lopata* 2014), while tropomyosin is common in shellfish (*Chinnappan et al.,* 2020). The cross-allergic reaction to fish and shellfish is high but variable (*Wang et al.,* 2020). With 90% of fish allergy patients reacting to parvalbumin, it is the most common clinical cross-reactive fish allergen (*Lim et al.,* 2008).

The allergenicity of parvalbumin has been studied in a number of fish species and as of 2012, the allergome database (www.allergome.org) (Table 8) has 218 allergenic isoforms of fish parvalbumin listed, while only 27 of these isoforms are actually registered with the World Health Organization (WHO) or International Union of Immunological Societies (IUIS) (*Sharp and Lopata* 2014). For ingestion-related sensitization, a variety of fish allergens have been isolated and identified, but the fish proteins in aerosol relevant for allergic sensitization have yet to be fully defined. Other fish allergens, such as the hormone vitellogenin from Beluga caviar, have been identified in addition to parvalbumin (*Escudero et*

Table 8. Sources of allergens (fish, crustaceans and molluscs) and identified allergens Handbook of Food Allergen Detection and Control, (2015) — *www. allergen. org-allergen nomenclature*

Sources of allergens	Common name	Scientific name	Allergen
Fish	Baltic cod Mackerel Atlantic salmon	*Gadus callarias* *Scomber japonicas* *Salmo salar*	Gad c 1 Sco j 1 Sal s 1–9
Crustaceans	Brown shrimp Tiger shrimp American lobster Chinese lobster Red crab	*Penaeus aztecus* *Penaeus monodon* *Homarus americanus* *Panulirus stimpsoni* *Charybdis feriatus*	Pen a 1 Pen m 1,2,3,4,6,8 and 13 Hom a 1, 3 and 6 Pan s 1 Char f 1
Molluscs	Mussels Noble scallop Abalone Pacific oyster Squid	*Perna viridis* *Chlamys nobilis* *Haliotis midae* *Crassostrea gigas* *Todarodes pacifi cus*	Per v 1 Chl n 1 Hal m 1 Cra g 10101, 10102 Tod p 1

al., 2007) and collagen and gelatine isolated from skin (*Perez et al.,* 2008) and muscle tissues of fish (*Sakaguchi et al.,* 2000). The second major allergen seems to be tropomyosin (*Chinnappan et al.,* 2020; *Lopata et al.,* 2016). Other allergens, such as 40 kDa arginine kinase, which could be a new class of pan-allergens in invertebrates and the skin of some fish species (*Hamada et al*. 2003), have been found and characterized in malignancies in addition to tropomyosin (*García-Orozcoet al.,* 2007).

It is important to note that tropomyosin is not just an allergen in crustaceans; it has also been found in a variety of mollusc species, including mussels, oysters, squid and sticklebacks, making them key food allergens in the exposed population. Molluscs also contain allergens such as big chain myosin, haemocyanin, and amylase, in addition to tropomyosin (*Jin et al.,* 2015).

Soybeans and soybean products

Soybeans (also called soy and soya) cultivated under particular conditions are included in the functional food list, as are other legumes, since they are a good source of biologically active chemicals that can have a beneficial effect (*Popov-Raljić*, 2016). The prevalence of soybean allergy is lower than that of each of the other seven major allergens, which has been used to suggest that soybean could be removed from the Big 8 without causing public harm (*Messina and Venter,* 2020). Soybean protein allergy was the least common allergy in four adult surveys, while milk/dairy and shellfish allergies were the most common. Soybean allergy was found in 0.1% of the population and 0.6% of the population. Soybean allergy was twice as common (0.5%) and similar to wheat allergy in the US NIAID-Children study, while milk/dairy allergy was still 3.8 times more common than soy allergy. Finally, the prevalence of soybean allergy in Canada (0.32%) was in the middle of that found in the two US surveys (*Gupta et al.,* 2019). In general, children with soy food sensitivities tend to outgrow their allergies).

The main allergens in soybean are: gly m 1–8, hydrophobic protein from soybean, defensin, profilin, pathogenesis-related protein, pr-10, bet v 1 family member, beta-conglycinin (vicilin, 7s globulin), glycinin (legumin, 11s globulin), seed biotinylated protein and 2s albumin. Gly m 4 is a major soy allergen, followed by Gly m 5 and Gly m 6 (*Holzhauser et al.,* 2009).

According to EFSA research (*EFSA*, 2014), people who are allergic to peanuts had a greater rate of anaphylactic reactions to soybean protein. In a randomly selected population in Europe, the prevalence of clinically diagnosed soybean allergy was minimal. For pollen allergen Bet 1 v and bovine

Table 9. Soybean and soybean-based products — *Popov-Raljić et al.* (2017), *The German Federal Institute for Risk Assessment (BfR), https://www.bfr.bund.de/* (2020)

Allergen and reference dose (mg)	Prevalence and severity	Some derivatives (additives) and allergen-containing foods that can cause allergic responses
Natural blends of tocopherol (E 306), natural D-alpha tocopherol, D-alpha tocopherol acetate, D-alpha tocopherol succinate, isolated phytosterols and phytosterol esters from soybean oil, in addition to fully refined soybean oil and fats  Reference dose = 0.5 mg protein **(VITAL 3.0, 2019, ED_{01})**	Children are more likely to have a soybean allergy, but they usually outgrow it by the age of two. This allergy can sometimes affect adults. Anaphylactic reactions are extremely infrequent, and most symptoms are mild. There is a possibility of allergenic cross-reactivity between soybeans and other legumes, particularly peanuts, and there have been cases of soybean and cow's milk cross-reactivity.	✓ Soybean flour ✓ Soybean tofu ✓ Soybean protein isolates ✓ Soybean protein concentrate ✓ Soybean formula for infants ✓ Soy sauce

Table 10. Foods that may contain soybean and labels that may indicate the presence of soybean in food
Steinman (1996), Aleksic and Popov Raljić (2015)

Foods that may contain soybean	Labels that may indicate the presence of soybean in food
Baby food	Arabic gum
Pastry	Protein emulsifier, crude soy lecithin
Pudding	Hydrolysed vegetable protein
High protein bread	Lecithin, a protein emulsifier
Minced meat	Soy flour, protein emulsifiers, nutritional supplements
Sausages	Monosodium glutamate
Dehydrated and canned soups	Protein supplement
Chocolate	Soy lecithin
Cakes and biscuits	Soy protein, crude soy lecithin
Oils	Soy protein isolated or concentrated
Hot dog	Soy sauce
Ice cream	Stabilizer
Liquid meal replacements	Starch
Salad dressing	Stabilizer
Sauce (Soy sauce, Worcestershire sauce sweet and sour sauce, tamari sauce etc.)	Tofu
Tofu	Vegetable starch

casein, serological and clinical cross-reactions between soybean and other legumes have been documented.

Table 9 shows a summary of the basic allergenic data for soybean and soybean products (prevalence and severity, as well as foods in which soybean can be found).

Soybean protein products are divided into three categories: additives (soybean flour, semolina, concentrate, protein isolate and hydrolysate), traditional products (soy sauce, miso, tempeh, natto, fermented tofu, unfermented tofu, soy milk and various beverages), and textured soybean products (textured snacks, chunks, structured meat analogues, protein fibre and meat analogues with high moisture content) (*Popov-Raljić*, 2016).

Soybean has a variety of allergenic proteins, with the major proteins glycine and conglycin serving as the primary allergens. Soybean, or its protein lecithin, is often a risk of allergy transmission due to its nearly infinite use in food production. Soybean products are available in a variety of forms to the food industry, including grain, flour, oil, emulsifier, protein supplement and stabilizer. As demonstrated in Table 10, it is typically listed as "hydrolysed vegetable protein" or "lecithin" in the ingredient list.

As a result, because soy is used in a wide range of foods, its declaration and labelling is a major issue. It is commonly found in ready-to-eat foods as a by-product of some of the minor ingredients. For example, if a ready-made/prepared food contains additional margarine, it is noted in the ingredient list, but mention may not be made of the fact that this product (margarine) contains soy or soy derivatives. Soybeans are an important source of oil. Although extracted soybean oil is thought to be safe for consumption, it is possible that a small amount of soy protein will be present (*Aleksić and Popov-Raljić*, 2017).

Peanuts and peanut products

Peanut allergy is a common, long-lasting, and potentially fatal food allergy that is becoming more common in Western countries. One of the most prevalent types of IgE-mediated food responses is peanut allergy (*EFSA*, 2014). It starts early in childhood, is most commonly diagnosed between the ages of 6 and 24 months, is more persistent than milk or egg allergies, and only 20% of patients gain tolerance to peanuts (*Medsen et al*., 2014). Table 11 shows the basic characteristics, distribution, and various food/gourmet goods in which peanuts and peanut products can be found.

So far, 18 peanut allergens have been isolated: Ara h 1 – cupin, Ara h2 – conglutin (2S albumin), Ara h3 – cupin (all three allergens are major peanut allergens), Ara h 4 – renamed as Ara h 3.02, number not available for future submissions, Ara h 5 – profilin, Ara h 6 and Ara h 7 – conglutin, Ara h 8 – pathogenesis–related protein, PR-10 − bet v1 family member, Ara h 9 – nonspecific lipid-transfer protein type 1, Ara h 10, 1, 14 and 15 – oleosins, Ara h 12 and 13 – defensins, Ara h 16 and 17 non-specific lipid transfer protein 2 and 1 and Arah 18 − cyclophilin, peptidyl-prolyl cis-trans isomerase (www. allergen.org/allergen nomenclature).

Because peanuts contain structurally comparable proteins and share common epitopes with other legumes like peas, beans, husks and lentils (*Vereda et al*., 2011), people with peanut allergy demonstrate allergic serological cross-reactivity with other legumes in the family (*Jensen et al.*, 2008).

Table 11. Peanuts and peanut products — *Popov-Raljić et al. (*2017), *The German Federal Institute for Risk Assessment (BfR), https://www.bfr.bund.de/* (2020)

Allergen and reference dose (mg)	Prevalence and severity	Some derivatives (additives) and allergen-containing foods that can cause allergic responses
Peanuts and peanut products  Reference dose = 0.2 mg protein **(VITAL 3.0, 2019, ED_{01})**	A large percentage of people who are allergic to peanuts, as well as other nuts, have an allergenic cross-reaction with other legumes like soy and beans. Heat treatment, particularly roasting, makes peanuts more allergenic.	✓ Unrefined, cold-pressed peanut oil ✓ Peanut butter ✓ Peanut flour ✓ Different peanut protein products ✓ Refined peanut oil

Peanut allergy management now consists of rigorous avoidance of peanut eating and the use of rescue medication in the event of incidental peanut ingestion. However, due to its extensive use as a food ingredient in packaged goods as well as restaurant and catering meals, complete avoidance of peanut is challenging (*Muraro et al*., 2014; *Remington et al*., 2020).

Nuts

Nuts come in a variety of forms, ranging from raw seeds to baked appetizers. In the EU, the average daily consumption of nuts and peanuts was 2.23 g for the entire population. From northern to southern Europe, total nut consumption ranged from 0.61 g per day in Sweden to 4.83 g per day in Spain. The

Table 12. Nuts — *Popov-Raljić et al.* (2017), *Economics of Agriculture/Ekonomika Poljoprivrede The German Federal Institute for Risk Assessment (BfR), https://www.bfr.bund.de/(2020)*

Allergen and reference dose (mg)	Prevalence and severity	Some derivatives (additives) and allergen-containing foods that can cause allergic responses
Almonds, hazelnuts, walnuts, cashew nuts, pecan nuts, Brazil nuts, pistachios, macadamia nuts and their products.  Except for nuts used in distillation and agriculturally produced ethyl alcohol for strong alcoholic and alcoholic beverages. Reference dose = 0.03 mg (walnut) Reference dose = 0.05 mg (cashew nuts) **(VITAL 3.0, 2019, ED_{01})**	Almonds, hazelnuts, walnuts, cashews, pecans, Brazil nuts, pistachios, and macadamia nuts are some of the most popular nuts. Macadamia nuts and their derivatives are a common source of allergies and can induce anaphylaxis responses in persons who are allergic to them.	✓ Nut Butter ✓ Pralines (hazelnuts) ✓ Marzipan ✓ Almond paste ✓ Walnut oils ✓ Worcestershire sauce (some brands contain walnuts)

most popular nuts in Europe are walnuts, almonds, pistachios, and hazelnuts (*Jenab et al*., 2006). This is a prevalent cause of dietary allergies in both infants and adults, and the clinical reaction can be fatal. In the entire UK population, 1.7% of people had a documented allergy to nuts and almonds. Some individuals (around 9%), including some who have had previous severe reactions, outgrow this type of allergy (*Fleischer et al*., 2005). Stone fruit allergies, like fish and peanut allergies, last a lifetime, and most stone fruit allergens are homologous to one another, resulting in frequent cross-reactivity. It is estimated that 20–50% of people allergic to peanuts also have a nut allergy (*Sicherer et al*., 2003).

Table 12 shows the basic characteristics, distribution and individual food/gastronomic products in which nuts can be found.

Walnuts have been proven to be a contributing factor in 1/3 to 1/4 of all food-related anaphylaxis responses (*Cianferoni and Muraro*, 2012). In black walnut (*Juglans nigra*), the most common allergens are jug n1 to n4, vicilin seed storage protein, legumin and 2S albumin seed storage protein, while for walnut (*Juglans regia*), the most common allergens are jug r1 to r8 (*EFSA*, 2014, www. allergen.org/ allergen nomenclature).

Conclusion

Food allergies are a major public health issue. Allergic reactions range from gastrointestinal problems and skin irritation to anaphylaxis, shock, and death. To avoid allergic responses, allergy sufferers must avoid foods containing allergenic ingredients. As a result, customers rely on food labels to inform them of the presence of allergenic substances. Food makers must create, implement, and maintain the required controls to guarantee that allergens that are intended to be present in a food are reported on the label and that unintended allergies are not present. Advisory words such as “may contain [allergen]” or “produced on equipment that also processes [allergen]” are not sufficient to prevent allergen contact. Allergen management will be achieved through the use of prerequisite programs as well as HACCP plan controls that ensure accurate product labelling. As a result, in Serbia, the National Allergen Strategy (NAS) must be developed in collaboration with key stakeholder organizations in order to improve the health and quality of life of Serbians with allergic diseases, and to ease the burden of allergic diseases on individuals, healthcare services and the community.

Alergeni u hrani – opasnost u sistemu bezbednosti hrane

Jovanka Popov Raljić, Milica Aleksić, Vesna Janković

Apstrakt: Alergeni u hrani javljaju se u poslednje dve decenije kao prikriveni oblik pretnje koja značajno ugrožava javno zdravlje, a njihovo obeležavanje na prehrambenim proizvodima, pićima i proizvodima koji nisu prethodno upakovani je jasno definisano zakonskim propisima. Alergija na hranu (FA) je hronično stanje opasno po život koje značajno narušava kvalitet života. FA predstavljaju značajan zdravstveni problem koji pogađa decu i odrasle i predstavlja značajan teret za zdravlje, zdravstveni sistem i ekonomije u razvoju. FA se definiše kao štetni zdravstveni efekat koji proizilazi iz specifičnog imunološki posredovanog odgovora koji se javlja prilikom konzumiranja određene namirnice, a koja može biti posredovana IgE antitelima specifičnim za hranu, ćelijski mehanizam ili oba. Odgovarajuće upravljanje alergijama na hranu postalo je problem za prehrambenu industriju zbog sve većeg broja osoba sa alergijama na hranu.

Ključne reči: *alergije na hranu, alergeni, velikih 8.*

Disclosure statement: No potential conflict of interest was reported by authors

Acknowledgement: The study was supported by Ministry os Education, Science and Technological Development of the Republic of Serbia, according to the provisions of the Contract on research financing in 2022, No 451-03-68/2022-14/200050 dated February 4th 2022.

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www. allergen. org-allergen nomenclature

Paper received: December 9th 2022.
Paper corrected: May 26th 2022.
Paper accepted: April 1st 2022.