

A Contemporary Review of Seafood Allergy

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Abstract Seafood is common item in the world diet; Asian countries have the highest rates of fish consumption in the world, which is higher than world average. Several studies have been conducted on the epidemiology and clinical characteristics of seafood allergy in different countries, and some of the fish and seafood allergens unique to those regions have been characterized. Review on published data showed that seafood allergy is very ubiquitous in some regions of the world. Fish and shellfish are the most common seafood that cause adverse allergic reactions among nations; the symptoms ranged from oral allergy syndromes to urticaria and anaphylaxis. The major identified allergens are parvalbumin in fish and tropomyosin in shellfish. Nevertheless, such studies are lacking from some regions with high fish and seafood consumption. Furthermore, the published data are mostly from small groups of populations, which large-scale epidemiological studies need to be performed.

Keywords Seafood · Allergy · Allergen · Prevalence · Clinical symptoms

Introduction

True food allergies are immune-mediated systemic allergic reactions to certain foods. According to the Food and Drug

Administration (FDA) [1], true food allergies affect less than 2% of the adult population and 2–8% of children, which most childhood food allergies are found in young infants and children under 3 years old. However, the number of people with food allergies appears to be increasing, especially among children. Reactions to a food allergen may range from uncomfortable skin irritations to gastrointestinal distress to respiratory involvement to life-threatening anaphylaxis [2].

Fish, egg, milk, and crustaceans represent the animal kingdom in the “big eight” group of food allergens [3]. The majority of food allergic patients react to these foods. Some of food allergens are similar in Asian and Western countries. For example, milk and egg allergy seem to be universal to all regions [4]; nevertheless, fish and seafood are more common to some regions [5, 6]. As consumption of seafood increases worldwide, immediate hypersensitivity reactions to seafood have become an important issue [7, 8]. Seafood allergy is very common in Asian countries where allergic reactions to seafood and particularly shellfish are significant among children and adults [9]. Asia is the world’s most populous continent, with a population of almost 4 billion people and many emerging economies. It has one of the highest rates of fish consumption in the world, with an estimated average annual consumption of 24.9 kg per capita compared with a world average of 16 kg per capita [10]. The first intake of seafood seems to be very early in life in the Asian diet, with an average age of as low as 7 months.

Seafood consumption and consequently allergy to it has also been increased in other continents. The rate of seafood allergy in allergy referral populations and among individuals with food-induced anaphylaxis has been reported from different locations in the USA, Europe, and Africa [8, 11–28]. This article reviews the occurrence of seafood allergies

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in different countries from around the world, and a brief description of the allergenic components present in fish and seafood from those regions is presented.

The Prevalence and Clinical Symptoms of Seafood Allergy in Different Continents

According to recent epidemiological data from the International Study of Asthma and Allergies in Childhood (ISAAC) phase III, asthma and allergic rhinitis have increased in several areas, mostly in low- and middle-income countries. The prevalence of allergic diseases in Asia increased from 0.8% to 29.1% for asthma and from 5% to 45% for allergic rhinitis as communities adopted modern lifestyles and became urbanized [29]. The most recent prevalence data from Asia has highlighted seafood as a significant sensitizer in up to 40% of children and 33% of adults [30]. Studies on humans demonstrated that biologically active fish allergens can be detected in serum samples as early as 10 min after ingestion. These studies highlight that minute amounts of ingested seafood allergens can quickly trigger allergic symptoms [30]. Fish and seafood also represents one of the most important causes of immunoglobulin E (IgE)-mediated hypersensitivity, especially in countries where the majority of the populations lives on fishing and where fish is the mainstay of the diet [31]. In allergic individuals, fish ingestion can provoke diarrhea, angioedema, or severe anaphylactic reactions. Inhalation of vapors generated during the cooking of fish may cause asthma, and skin contact can lead to urticaria and dermatitis [32].

Several population-based studies have been conducted on the fish and seafood allergies in different countries. The majority of those studies focused on children, who are the most sensitive group to allergies. In Southeast Asia, studies have been reported from Malaysia, Thailand, Singapore, Indonesia, and Philippines; while from other parts of this wide and populous continent, reports can be found from Japan, Korea, China, Hong Kong, and Taiwan. Published surveys on prevalence of seafood allergy are also available from different parts of the USA, Africa, Germany, Italy, Spain, Sweden, Switzerland, Portugal, and UK (Table 1).

Asia

Malaysia

An observation was conducted on the incidence of food allergy in patients with nasal congestion and rhinorrhea attending the Otorhinolaryngology Clinic, Kuala Lumpur, Malaysia [33]. The skin prick test (SPT) was used to evaluate 11 foods common to the Malaysian diet. Of the

patients with rhinitis, 48% had positive SPT results to foods. The most commonly implicated foods were shrimp (48%) and rice (30%), which are common in the Malaysian diet. Among Malaysian patients with allergic rhinitis and asthma, shellfish and fish were the most common food.

Thailand

In an earlier study of asthmatic children in an allergy clinic in Bangkok, Thailand, 7.6% of patients reported precipitation of asthma by foods. Studies in Thailand indicated that seafood is the most common cause of food allergy and shrimp was one of the most common foods to cause positive skin allergy [4]. Fish and other seafood are taken early during childhood in Thailand. An investigation on prevalence of food allergy among Thai children showed that crustaceans (particularly shrimps) were the most common seafood that causes adverse food reactions among older children [34]. Observation on clinical manifestations of seafood allergy among Thai patients showed that start of symptoms ranged between 5 min to 5 h (mean 61.55 min). The most common symptom was urticaria (60%) and oral allergy syndrome (37.5%), whereas the most common causative agent reported was shrimp (68.7%). Study by Chinratanasit et al. [35] on Thai shrimp allergic children showed that there were subpopulations of shrimp allergic patients that are allergic to only freshwater shrimp, *Macrobrachium rosenbergii*, but can tolerate seawater shrimps. On the other hand, some patients are allergic to only seawater shrimp (*Penaeus monodon*). Jirapongsananuruk et al. [36] studied the clinical characteristic of patients with anaphylaxis in Thailand. They reported that the annual occurrence of anaphylaxis increased from 9.16 per 100,000 admitted persons in 1999 to 55.45 per 100,000 admitted persons in 2004. Foods were the second most common cause of anaphylaxis and seafood was the most common cause of food-induced anaphylaxis (46%). Study on the diagnostic SPT to crude shrimp extract and cooked shrimp showed 73% positive allergy in children [37].

Singapore

The results of a study of IgE sensitization to foods measured by SPTs or serum IgE anti-food antibodies showed there was relatively high incidence of shellfish allergy in Singapore [4]. In a study on pattern of food-induced anaphylaxis in children from Singapore, crustacean seafood was second most common food-allergen source (34 cases, 27%) with the main symptom of urticaria [38]. Seafood (crustaceans and mollusks) and fish comprised 66.7% and 3.3% of food-induced anaphylaxis in Singapore [39].

Table 1 Prevalence and clinical symptoms of seafood allergy in different regions

Country	Seafood source	Prevalence	Clinical symptoms	Study year	Reference
Malaysia	Shrimp	48%	Nasal congestion and rhinorrhea	2000	[33]
Thailand	Shrimp	7.6%	skin allergy	1997	[4]
		68%	Urticaria/oral allergy syndrome	2005	[34]
	Seafood	9.16/100,000	Anaphylaxis	1999	[36]
		55.45/100,000	Anaphylaxis	2004	[36]
	Crude shrimp extract/cooked shrimp	73%	Skin allergy	2008	[37]
Singapore	Crustacean seafood	27%	Urticaria	1999	[38]
	Crustaceans and mollusks	66.7%	Anaphylaxis	2005	[39]
	Fish	3.3%	Anaphylaxis	2005	[39]
	Crustaceans and mollusks	64.9	Periorbital angioedema	2007	[40]
		44.6%	Dyspnea/wheezing/urticaria		[40]
Korea	Fish	12.5–14.9%	Atopic dermatitis	1995–2000	[6]
	Crab, lobster, shellfish	7.6–16.6%			[6]
	Seafood	2.9%	Anaphylaxis	2008	[43]
	Finfish, conger, squid, whelk, tuna	100%	Urticaria	2009	[44]
		30%	Abdominal pain		[44]
		30%	Anaphylaxis		[44]
Japan	Shellfish	2–6%	Shellfish hypersensitivity	1997	[4]
	Seafood	10.6%	Immediate-type allergic reaction	2000	[45]
	Shrimp	9.4%	Allergic rhinitis, atopic dermatitis, bronchial asthma	2002	[47]
	Crab	6.5%			[47]
	Mackerel	5.6%			[47]
	Shellfish	2.1%			[47]
	Sea urchin	1.4%			[47]
	Roe	1.4%			[47]
	Fish	85%	Oral swelling and pain	2004	[48]
	Fish and shellfish	56%			[48]
	Shellfish	27%			[48]
China	Shrimp	70.3%	–	1985	[51]
	Crab	70.3%	–		[51]
	Crayfish	42.1%	–		[51]
	Squid	37.7%	–		[51]
Hong Kong	Seafood	71%	Anaphylaxis	2005	[53]
Taiwan	Shrimp	34.9%	Shrimp hypersensitivity	1999	[54]
	Shrimp, crab	15%	Atopic dermatitis	2004	[55]
	Seafood	–	Respiratory symptoms	2007	[56]
	Shrimp, crab, and shellfish	50.1%	–	2006	[57]
Norway	Crab and shrimp	–	Breathlessness	2001	[20]
Spain	Lobster	–			[20]
Germany	Atlantic shrimp	85.4%	Allergic asthma	1995	[16]
Italy	Snail	28 cases	Asthmatic symptoms	1996	[17]
	Shellfish	60%	Gastroenteritis	2002	[22]
Sweden	Seafood	20.28%	–	2001	[12]
Switzerland	Fish	84%	Oral allergy syndrome	1999	[19]
Portugal	Fish and crustaceans	–	Atopic symptoms, anaphylaxis	2007	[11]
UK	Queen and king scallop	–	Asthma and urticaria	2006	[23]
USA	Oysters and crustacean	–	Oysters and crustacean sensitivity	1987	[14]
	Shrimp	30%	Positive skin test	1988	[15]
		82%	Positive skin test	1994	[13]

Table 1 (continued)

Country	Seafood source	Prevalence	Clinical symptoms	Study year	Reference
Africa	Clam and shrimp	4–7%	Rhinoconjunctivitis and asthma	1995	[8]
	Any seafood	2.3%	Dyspnea, throat tightness	2004	[21]
	Fish	0.4%	"	"	[21]
	Shellfish	2%	"	"	[21]
	Shellfish and crustacean	1.3–1.9%	–	2007	[25]
	Abalone	65.78%	Immediate skin reaction	1997	[18]
	Prawn	46.7%			[18]
	Crayfish	43.8%			[18]
	Abalone	35.2%			[18]
	Black mussel	33.3%			[18]
	Hake	24.8%			[18]
	Yellowtail	21.9%			[18]
	Salmon	15.2%			[18]
	Mackerel	15.2%			[18]
	<i>Anisakis</i> in fish	6%	Oral and skin symptoms	2008	[24]
	Canned fish and fishmeal	26%	Ocular–nasal symptoms	2008	[26]
		16%	Asthma symptoms		[26]
	Pilchard	100%	Gastrointestinal, respiratory, and dermatological symptoms	2009	[27]
	Anchovy, hake, Snoek	40%			[27]
	Yellowtail	20%			[27]
	Raw and cooked pilchard	100%	Occupational allergy and asthma	2011	[28]

The patient characteristics, clinical features and causative foods in 74 consecutive adult patients with immediate food hypersensitivity were studied in Singapore [40]. Crustaceans and mollusks were the most common causative foods. Prawn and crab were the most commonly implicated crustacean, and limpet the commonest culprit mollusk. The main symptoms were periorbital angioedema (64.9%), dyspnea/wheezing (44.6%), and urticaria (44.6%). A total of 66% of the patients developed anaphylaxis, and 45.9% had concomitant allergic rhinoconjunctivitis, asthma, eczema, or combinations of these atopic diseases. Chiang et al. [9] studied food protein sensitization patterns in a population of Singaporean children with possible food allergy. Shellfish and fish sensitization was 39% and 13.2%, respectively. The median reported age of first exposure to fish and shellfish was 6 and 12 months, respectively. The mean age at presentation of children with shellfish hypersensitivity was at 6.7 years of age. The likelihood of shellfish sensitization was increased in children with concomitant sensitization to cockroaches.

Korea

Shrimp, mackerel, abalone, and lobster were the most common food allergens sensitized in Korean population with sensitization rate of more than 1% [41]. An extensive survey on school children 6 to 14 years has been done by

Oh et al. [6] on prevalence of atopic dermatitis and food allergy with the comparison of prevalence between 1995 and 2000 throughout Korea. They also determine the correlation of prevalence between atopic dermatitis and food allergy. Their study showed that the prevalence of atopic dermatitis in Korean school-aged children was increased during the period of 1995 to 2000. The 12-month prevalence of atopic dermatitis and food allergy were higher in Seoul than in any other provincial cities in 1995; however, the prevalence of both diseases in Seoul and provincial centers was similar in 2000. Fish (14.9% in 6–12 year olds, 12.5% in 13–15 year olds) and seafood such as crab, lobster, and shellfish (7.6% in 6–12 year olds, 16.6% in 13–15 year olds) were identified as most common food allergen. A nationwide study indicated a reduced risk of asthma symptom prevalence in Korean children with an increase intake of natural seafood, fruit, and vegetables was significantly related to reduced asthma [42].

A more recent study by Yang et al. [43] on the incidence and mortality rate of anaphylaxis in Korean patients who visited the allergy clinic and emergency department showed that, among 978,146 patients, 138 (0.014%) had anaphylaxis. The total mortality rate of anaphylactic patients was 0.0001%. A 13.2% of the cause of anaphylaxes was food-dependent exercise with 2.9% related to seafood consumption. Any fish or cephalopod species can be parasitized by third stage *Anisakis* larvae. Codfish, hake, sardines,

anchovies, salmon, tuna, and squid are among the most frequently parasitized species. The ingestion of third-stage *Anisakis* larvae can cause anisakiasis in humans. Choi et al. [44] reported the clinical features of 10 *Anisakis* allergy cases in Korea. Sensitization to *Anisakis* was confirmed by detecting serum specific IgE to *Anisakis simplex*. The most common manifestation of anisakiasis was urticaria (100%), followed by abdominal pain (30%), and anaphylaxis (30%). All patients presenting with these symptoms also exhibited high serum-specific IgE (0.45–100 kU l⁻¹) to *A. simplex*. About 90% of patients exhibited atopy and increased total serum IgE levels. The fish species suspected of carrying the *Anisakis* parasite were flatfish (40%), congers (40%), squid (30%), whelk (10%), and tuna (10%). Therefore they considered *A. simplex* as a possible causative food allergen in adult patients presenting with urticaria, angioedema, and anaphylaxis following the consumption of raw fish or seafood.

Japan

Shellfish hypersensitivity patient numbers were reported to gradually increase in Japan. It is estimated that 2–6% of children under the age of 14 years had shellfish hypersensitivity [4]. Study on the frequency of immediate-type food allergy in children in Japan showed that that 12.6% of the children experienced immediate-type allergic reaction. Seafood was the third most common food allergen with frequency of 10.6% [27, 45]. Sakaguchi et al. [46] investigated IgE antibody to fish gelatin in children with fish allergy in Japan. Their study showed that out of 10 patients with fish allergy, three had specific IgE to fish gelatin. Out of two patients with fish allergy and bovine gelatin allergy, all had specific IgE to fish gelatin. Out of 15 patients with atopic dermatitis and specific IgE to fish meat, five had specific IgE to fish gelatin. While, there was cross-reactivity among gelatins from various fishes, there is little cross-reactivity between fish and bovine gelatins. They realized that since some fish-sensitive patients possessed IgE antibody to fish gelatin, fish gelatin (type I collagen) might be an allergen in subjects with fish allergy.

In a study on the actual situation of food allergy in 2053 Japanese university students, food allergy was noted in 5.2% of subjects, with a higher prevalence in female students. Allergy to seafoods, such as shrimp (9.4%), crab (6.5%), mackerel (5.6%), shellfish (2.1%), oyster (1.4%), sea urchin (1.4%) and roe (1.4%), was frequently noted. Among students with a food allergy, the proportion of those with allergic rhinitis, atopic dermatitis and bronchial asthma was 45.8, 29.0 and 12.1%, respectively [47]. Seafood was reported as a major allergen in adults with food hypersensitivity in Japan. Shibata and Nishima [48] measured serum specific IgE to salmon roe, Alaska pollack roe, clam, oyster

and scallop in children with seafood allergy to investigate sensitization to these allergens. Patients with fish and/or shellfish allergy (41) were divided into three groups; group 1 (15 cases): fish only, group 2 (13 cases): fish+shellfish, and group 3 (13 cases): shellfish only. Positive IgE to one or more mollusks were identified at 85% in group 3, 56% in group 2 and 27% in group 1. Of the three groups, one third had positive IgE to one or both fish roe. Of these patients, 12 had history of hypersensitivity to mollusks and eight were positive IgE to all three mollusks tested. Three patients with anaphylaxis to salmon or Alaska pollack roe had positive IgE to both fish roes. A case of shrimp allergy whose serum IgE reacted with both crustaceans and mollusks has been reported from Japan. The patient with shrimp allergy developed oral swelling and pain accompanied with an uncomfortable feeling after ingestion of scallops followed by intensive exercise. Laboratory investigation showed that she had serum immunoglobulin (Ig)E molecules reacting with several kinds of crustaceans and mollusks, including shrimp, crab and scallops.

Immunoblotting revealed that tropomyosin (TM) was the major seafood allergen in Japan [49]. Sato et al. [50] reported two cases of anaphylaxis due to fish hypersensitivity in exclusively breastfed infants from Japan. The first case developed whole-body rash after his mother took raw fish. His SPT was positive to horse mackerel, mackerel, salmon and codfish. The second case developed rash and cough and vomiting after mother took seafood. Blood examination revealed high titer of specific IgE to sardine and codfish in his serum. SPT was also positive to sardine. While only small amount of allergens was detectable in breast milk, they showed systemic immediate type food allergy due to small amounts of food allergens included in breast milk which is very rare.

China and Hong Kong

In intra-dermal skin tests to allergen extracts in 763 patients from Guangzhou, China, a high incidence of positivity to shrimp (70.3%), crab (60.8%), crayfish (42.1%) and squid (37.7%) were detected [51]. A survey on allergy prevalence in a population from China found that the common identified allergens were fish, shrimp, crab and seaweed [52]. Study on local Chinese population in Hong Kong showed high incidence of seafood allergy (71%) in patients with anaphylaxis [53].

Taiwan

A moderate incidence of shellfish sensitisation was noted in infants and young children and fish was not an important food allergen in Taiwan [4]. Tsai and Chen [54] studied the relation of different food allergens to different age of 1,070

cases of asthmatic patients in Taiwan. Results showed that there were 34.9% patients allergic to shrimp. The age with highest incidence rate to shrimp allergy was 11–20 years old. In this age group, there were 51.9% patients allergic to shrimp, 42.9% of them were moderate hypersensitivity and the rest were mild hypersensitivity. They concluded seafood allergy occurred later and more severe than other food allergies. Huang et al. [55] reported food allergies as causal factors for atopic dermatitis in 43% of children aged 0–2 years and around 30% in other age groups in Taiwan. Seafood allergy (shrimp, crab) accounted for about 15% of food allergies in children aged 3–11 years and increased gradually in adolescents and young adults. Study on the association of diet with respiratory symptoms and asthma in school children in Taipei, Taiwan indicated that consumptions of seafood was positively associated with all the respiratory symptoms (persistent cough, chest tightness, wheezing with cold, wheezing without cold, and dyspnea-associated wheezing) except for physician-diagnosed asthma [56].

In a survey on effect of age on response to different allergens in 4,411 allergic patients in southern Taiwan, 50.1% samples showed a positive response. Shrimp, crab, and shellfish were the main allergens in the groups aged 7–12, 13–18, and more than 18 years. Among seafood allergens, shrimp was the most common in all age groups, followed by crab [57]. Study on 498 children (aged 2–16 years) with atopy in central Taiwan showed low positive prevalence (<12%) for food allergens including shrimp, crab, milk, egg white, peanut, wheat, soybean, codfish, yeast, and melon [57].

Indonesia and Philippines

Not very many studies were done in Indonesia, Philippines, and other Asean countries. Partana et al. [58] reported high incidence of positive reactions to shellfish and fish in Indonesian children. A very high incidence of shellfish has also been reported in children from Philippines [4].

Europe

A cross-sectional epidemiological study involving 12 European countries has been carried out by Woods et al. [20]. Participants of 20–44 years of age answered a detailed interviewer-administered questionnaire and took part in blood, lung function, and SPTs. The dietary questionnaire asked whether they ever had an illness or trouble caused by eating a particular food or foods, and the respondents were then asked to list the foods and symptoms in order to distinguish between symptoms of food poisoning and food allergy or intolerance. Of the respondents, 12% reported food allergy/intolerance (range 4.6% in Spain to 18% in Sweden). Of the 3,334 participants, 19% indicated that they

had experienced “illness or trouble” caused by eating a particular food or foods. A total of 53 different food items were reported as being associated with the reporting of breathlessness from food. Fish (white, cod, and plaice) was among the most commonly reported foods. Breathlessness was reported as symptom following consumption of crab and shrimp, and lobster by respondents from Norway and Spain, respectively.

Germany

Crespo et al. [16] studied IgE-antibody reactivity to boiled Atlantic shrimp (*Pandalus borealis*) and German cockroach (*Blattella germanica*) in sera from 89 German patients. IgE serum levels to both anti-shrimp and anti-cockroach allergens were found to be positive in 85.4% of tested sera. A positive anti-cockroach IgE was very rare in the absence of detectable anti-shrimp IgE. This research showed that boiled Atlantic shrimp extract inhibited CAP with German cockroach, and vice versa. The strongest IgE binding for both allergenic extracts was between 30 and 43 kDa. They reported cross-reactivity between shrimp and German cockroach, which has an increasing role in allergic asthma.

Italy

A study on 28 patients from Italy who have asthma after consumption of snail showed that all patients also had asthma and/or rhinitis caused by house dust mite. Radioallergen sorbent test (RAST) analyses confirmed the combined sensitization to snail and mite. In the sera, IgE antibodies reactive with mussel and shrimp were detected, and most IgE antibodies against snail were cross-reactive with house dust mite. This study indicated that house dust mite was the sensitizing agent. TM played only a minor role as a cross-reactive allergen in these patients. They concluded that snail consumption can cause severe asthmatic symptoms in house dust mite-allergic patients [17].

Following outbreak of gastroenteritis in the province of Bari (Southeast Italy), in April 2002, Prato et al. [22] conducted a research to identify the cause of this outbreak. They used a retrospective cohort study in order to assess risk factors associated with illness. All households where a case occurred were included in the study. Eleven samples of mussels were collected from fish markets involved in the outbreak. One hundred and three cases, detected by means of active surveillance, met the case definition. Raw shellfish eating was the principal risk factor for the disease, as indicated by the analytic issues. Eleven samples of shellfish from local markets were tested for the presence or NVs; 54% were positive by nested polymerase chain reaction (PCR) and genotypes were related to that found in patients' stools.

Sweden

The allergenic relationship between nematode *A. simplex* (a common parasite on fish and other seafood) and four different dust mite species (*Acarus siro*, *Lepidoglyphus destructor*, *Tyrophagus putrescentiae*, and *Dermatophagoides pteronyssinus*) were studied. Serum samples collected from 69 Sweden farmers allergic to at least one of the dust mite species were analyzed for IgE to *A. simplex*. They found that 14 farmers had detectable levels of IgE antibodies to *A. simplex*. The IgE response to *A. simplex* was inhibited to various degrees in the studied sera by extracts of the dust mites *A. siro*, *L. destructor*, *T. putrescentiae*, and *D. pteronyssinus*. In blotting inhibition experiments, the IgE binding to several allergens in *A. simplex* was inhibited by each of the four mite extracts, especially by *A. siro* and *T. putrescentiae*, which completely inhibited the IgE binding to several allergens [12].

Spain

The study by Arlian et al. [59] on somatic extracts of *A. simplex* larva showed that it contains a large number of allergenic molecules. Antigen–antibody precipitins (12–16) were identified. There was significant variability between Spanish patients in their sensitivity and reactivity to these allergens. Autoradiography of crossed radioimmuno-electrophoresis gels showed that 18 different proteins bound IgE in patient sera. Individual patients had serum IgE directed at two to ten different allergens, in which five were recognized by more than 50% of the patients. No allergen was recognized by every patient, and no patient had serum IgE directed at all 18 allergens.

Taylor et al. [60] studied the possibility of passively aerosolized fish allergen in an open-air fish market using air sampling and a competitive IgE immunoassay. Fish allergens were specifically quantified by using pooled sera from fish-sensitive individuals from Spain. Allergen was quantified in all 39 fish market air samples. By using air sampling and an immunochemical analytic technique, fish allergen were detected in the air of an open-air fish market.

Switzerland

A research was conducted by Helbling et al. [19] with the aim of determination of potential cross-reactivity to different fish species using double-blind, placebo-controlled food challenges in fish-allergic adults in Switzerland. They compared skin test and RAST reactivity with the challenge response. A 74% of double-blind, placebo-controlled fish challenges resulted in the induction of objective signs that were consistent with an IgE-mediated response. The most common sign observed was emesis (37%); the most prevalent

subjective symptoms reported were compatible with the oral allergy syndrome (84%). Three subjects reacted to at least three fish species and one subject reacted to two fish species tested. This study indicated that clinically relevant cross-reactivity among various species of fish may exist.

Portugal

Carrapatoso et al. [11] conducted a study to characterize a group of patients with food anaphylaxis followed up in a food allergy outpatient department in Portugal during a 1-year period. Foods involved in the severe systemic reactions were identified, and atopic co-morbidities, occurrence of anaphylaxis in the study period, and the medication used were investigated. A standardized questionnaire and SPTs to airborne allergens (mites, moulds, cockroach, cat and dog dander, pollens, feathers, latex) and food allergens (egg, milk, seafood, mammals' and birds' meat, fruits, nuts, cereals, legumes, spices, and other vegetables) were performed. Serum-specific IgE to airborne and food allergens and/or prick-to-prick with natural food extracts were done in selected cases. Among the foods involved in anaphylaxis were crustaceans in four patients and fish in two patients.

United Kingdom

Barracough et al. [23] reported a case of occupational asthma and urticaria due to the queen scallop (*Chlamys opercularis*) and king scallop (*Pecten maximus*) in UK. A 40-year-old female worked in a shellfish-processing plant, handling king and queen scallops for 5 years described a 2-year history of work-related respiratory symptoms. The investigation showed that it was consistent with occupational asthma. RAST testing demonstrated evidence of specific sensitization (IgE) to queen and king scallop. There was also some cross-reactivity observed with other shellfish (prawns and crabs).

United States

Lehrer and McCants [14] investigated IgE-antibody reactivity to oysters and crustaceans in six oyster-sensitive, seven oyster- and crustaceans-sensitive, and 12 crustaceans-sensitive subjects from the USA. All six subjects with a history of only oyster sensitivity had minimal RAST reactivity to extracts of raw or boiled oysters. Of the seven oyster- and crustaceans-sensitive subjects and the 12 crustaceans-sensitive, oyster-tolerant, or unexposed subjects, three and six subjects, respectively, showed elevated RAST ratios to oyster. Elevated oyster RAST correlated with SPT reactivity to oyster but not with total serum IgE levels. Rabbit antisera to crustacean extracts detected

precipitating antigens present in extracts of raw or boiled oysters. Significant inhibition of the oyster RAST was obtained with oyster or crustacean extracts. Their study suggested that, in the diagnosis of oyster sensitivity, the RAST may not be useful and that oyster and crustacean contain common antigenic structures.

Daul et al. [15] studied on 30 American individuals with history of immediate adverse reactions after shrimp ingestion using double-blind, placebo-controlled shrimp-food challenges. Patients who did not exhibit a positive response (reproduction of objective symptoms) were administered an open challenge of 16 whole cooked shrimp. Positive challenge responses occurred in 30% of subjects; six of these subjects experienced a positive response during the double-blind phase. Of the 60% remaining subjects, 12 experienced generalized pruritus as their only symptom, whereas nine subjects had completely negative challenge responses. All placebo challenges were negative. Although a positive skin test was strongly associated with challenge symptoms, the shrimp prick skin test titration end-points were not different among the challenge groups. The levels of shrimp-specific serum IgG, IgA, and IgM levels were not different among the challenge groups. The composite of a positive shrimp prick skin test and elevated serum shrimp-specific IgE demonstrated a correct predictive value of 87% in this group of shrimp-sensitive subjects.

Daul et al. [13] used shrimp as a model food allergen to identify the allergens. They found that extracts from both shrimp (*Penaeus aztecus*) meat and cooking fluid contain a substantial and similar amount of allergenic activity. A 36 kDa allergen, in both extracts reacted with 28/34 (82%) sera from shrimp-sensitive, skin test, and RAST-positive patients. They named this allergen Pen a I; its amino acid composition was rich in aspartic and glutamic acids. A 21-residue peptide, obtained from endoproteinase Lys-C digested Pen a I, showed significant homology (60–87%) with the muscle protein TM from various species and origins such as fruit fly (*Drosophila melanogaster*). This study showed that TM is the major shrimp allergen.

An investigation was carried out in 60 exposed workers in the USA in order to confirm occupational asthma caused by clam and shrimp in a food company worker [8]. Prior to the production period of clam and shrimp, a medical and occupational questionnaire was carried out. The skin and RAST testing were done with common inhalants and clam, shrimp, crab, and lobster extracts before, during, and after the production period. Four (7%) subjects showed a history of rhinoconjunctivitis and two (4%) had a history of asthma during the period of clam production, whereas three (5%) subjects had rhinoconjunctivitis and two (4%) had asthma during the shrimp production. Three (5%) subjects had immediate skin reactivity to clam and nine (16%) subjects to shrimp. Four (7%) subjects had increased specific IgE

antibodies (RAST binding $\geq 3\%$) to clam and eight (14%) to shrimp. This study found significant associations between immunologic reactivity to clam and shrimp on the one hand and to crab and lobster on the other. Occupational asthma caused by clam was confirmed by specific inhalation challenges in one subject in addition to the index case. These two subjects showed skin reactivity and increased specific IgE antibodies to clam, shrimp, or both.

A comprehensive study by Sicherer et al. [21] estimated the prevalence of seafood (fish, shellfish) allergy in the US. They performed a nationwide, cross-sectional, random telephone survey by using a standardized questionnaire. They established the criteria were to define seafood allergy by report of convincing symptoms and physician evaluation. A total of 5,529 households completed the survey, representing a census of 14,948 individuals. Fish or shellfish allergy was reported in 5.9% of households and among individuals as 2.3% for any seafood allergy, 2% for shellfish, 0.4% for fish, and 0.2% for both types. This study showed that seafood allergy was more common in adults compared with children (2.8% vs. 0.6%) and in women compared with men (3.6% vs. 2%). Recurrent reactions were reported by 58%, dyspnea, or throat tightness by more than 50%, and 16% were treated with epinephrine. The rate of reactions to multiple fish among those with any fish allergy was 67%; for crustacean, the rate was 38%, and for mollusks, the rate was 49%; only 14% with crustacean allergy reported a mollusk allergy.

Villacis et al. [61] concerned on the possible allergic reaction to glucosamine-containing products and conducted a research to determine whether shrimp-allergic individuals can tolerate therapeutic doses of glucosamine. American patients (15) with a history of shrimp allergy were tested for both shrimp reactivity via a prick skin test and shrimp-specific IgE. All subjects tolerated 1,500 mg of both shrimp-derived and synthetic glucosamine without incident of an immediate hypersensitivity response. They concluded that glucosamine supplements from specific manufacturers do not contain clinically relevant levels of shrimp allergen and therefore appear to pose no threat to shrimp-allergic individuals.

Vierk et al. [25] reported the prevalence of self-reported food allergy, to identify the characteristics of food allergy reactions, and to describe the use of labels among adults with food allergy. They used the Food Safety Survey which is a list-assisted random-digit-dial survey of American consumers conducted periodically by the FDA (Administration's 2001 Food Safety Survey). The food allergy questions were cognitively tested with members of the Food Allergy and Anaphylaxis Network for clarity, completeness, and relevance of item content. The survey was conducted by using a nationally representative single-stage sample of telephone numbers. Persons who claimed of having any food allergy or

suspecting that they have a food allergy were defined as who self-reported food allergy. On the basis of additional questions, this group was further subdivided on the basis of whether they had received a doctor's diagnosis. Respondents were asked to identify what food or food ingredients to which they were allergic. The eight most common food allergens recognized by the FDA were milk, egg, wheat, soy, peanut, tree nuts, fish, and crustacean shellfish. Several questions on using food labels to manage food allergies were included in the survey. Results showed that the prevalence of self-reported food allergy was 9.1% among all survey respondents, with 5.3% of all respondents reporting a doctor-diagnosed food allergy. Prevalence of shellfish and crustacean food allergy, or both in this study was found to be 1.9% among respondents with self-reported food allergy and 1.3% among respondents with self-reported doctor-diagnosed food allergy. Although there was no difference in overall prevalence of food allergy by race/ethnicity, 44.1% of black respondents with self-reported food allergy reported a fish, shellfish, or crustacean food allergy compared with 24.0% of white respondents. Among respondents with self-reported doctor-diagnosed food allergy, 46.1% of black respondents vs. 30.1% of white respondents reported a fish, shellfish, or crustacean allergy. Several label issues, such as words on some ingredient lists being too technical or hard to understand and food labels not always alerting persons to new ingredients, were reported as serious or very serious obstacles for managing an allergy.

Africa

The study by Lopata et al. [18] reported the clinical and immunologic findings in South African patients with reported immediate and delayed adverse reactions to abalone (*Haliotis midae*). Allergic symptoms were assessed by a self-administered questionnaire in patients with abalone sensitivity. Specific IgE responses, SPTs, and lymphocyte proliferation assays to abalone and other mollusks were performed. Of the 38 patients in the study, 25 were first seen with immediate symptoms, and 13 had delayed reactions. Of the sera tested, 17 were RAST-positive. SPT responses with abalone extract were positive in all eight subjects with positive RAST responses and in 6 of 13 subjects with negative RAST responses. Of the subjects with positive RAST responses, five had positive results and demonstrated binding to two major allergens with molecular weights of 38 and 49 kDa. This study indicated a clear clinical and immunologic heterogeneity in patients reactive to abalone.

The range of allergy to South African bony fish (Class Teleostei), crustaceans, and molluscs was assessed by Zinn et al. [62] using a double-blind, placebo-controlled food challenge. Patients in the Western Cape were recruited by

means of a seafood allergy questionnaire. Subjects with reported allergy to hake, yellowtail, salmon, and mackerel were investigated by means of skin-prick tests, RASTs, and Western blot analysis. The four most common seafood species reported to cause adverse reactions were prawns (46.7%), crayfish (43.8%), abalone (35.2%), and black mussels (33.3%). The four most common bony fish species to cause reactions were hake (24.8%), yellowtail (21.9%), salmon (15.2%), and mackerel (15.2%). Bony fish showed a significant cause of clinical reactions to seafood in the Western Cape.

Nieuwenhuizen et al. [24] determined the prevalence of *Anisakis* sensitization and related symptoms among 578 workers in two fish-processing factories in South Africa. They used gene-deficient mice to determine the working mechanisms of *Anisakis* allergy. Sensitization to *Anisakis*, seafood, and common aeroallergens was determined by SPT. The prevalence of sensitization to *Anisakis* was higher than the prevalence of sensitization to fish (8% vs. 6%). *Anisakis*-specific IgE reactivity was associated with bronchial hyperreactivity and dermatitis and significantly increased with fish consumption. In mice, *Anisakis* infective larvae (L3) induced a striking TH2/type 2 response. Food-allergic-type reactions induced by oral challenge with *Anisakis* extract were absent in IL-4 receptor a knockout mice. This study showed that *Anisakis* sensitization in fish-processing workers is associated with allergic symptoms and correlates with high levels of fish consumption.

Later, Jeebhay et al. [26] proposed a broader study on the prevalence and host determinants of allergic symptoms, allergic sensitization, bronchial hyper-responsiveness, and asthma among the same population. They conducted a cross-sectional study on 594 workers in processing plants involved in pilchard canning and fishmeal processing. SPTs used extracts of common airborne allergens, fresh fish (pilchard, anchovy, maasbanker, mackerel, red eye), and fishmeal. Work-related ocular–nasal symptoms (26%) were more common than asthma symptoms (16%). The prevalence of atopy was 36%, while 7% were sensitized to fish species and 26% had NSBH. The prevalence of probable occupational asthma was 1.8% and fish allergic rhinoconjunctivitis 2.6%. Women were more likely to report work-related asthma symptoms and have NSBH, while men were more likely to be sensitized to fish and have airway obstruction. They concluded that the prevalence of occupational asthma to saltwater fish was lower than due to shellfish.

The antigenic cross-reactivity and the presence of oligomers and isomers of parvalbumin from five highly consumed fish species [pilchard (*Sardinops sagax*), anchovy (*E. encrasicolus*), hake (*M. merluccius*), snoek (*Thyrsites atun*), and yellowtail (*Seriola lalandi*) in Southern Africa were studied [27]. Parvalbumin from pilchard (*S. sagax*) was

found to display the strongest IgE reactivity among ten fish-allergic consumers. All ten subjects with known fish allergies following consumption were considered atopic seeing that they had a positive skin reaction to one or more common inhalant allergen. All these individuals demonstrated IgE specific to pilchard, while nine individuals displayed IgE reactivity to anchovy. Aside from gastrointestinal symptoms, most of them also reported respiratory and dermatologically related allergic symptoms. Fish-allergic subjects displayed the most widespread IgE reactivity to parvalbumin from pilchard. Yellowtail parvalbumin was recognized by two subjects, while parvalbumin from anchovy, snoek, and hake was recognized as an allergen in four fish-allergic subjects.

Following the study by Beale et al. [27], a research was conducted by van der Ventel et al. [28] to identify the allergenic proteins in raw and/or cooked fish that are responsible for causing occupational allergy and asthma following inhalation of fish aerosols in South Africa. They have developed the first mouse model of inhalant fish allergy and used it to characterize detailed immune responses to raw and cooked fish in comparison to natural parvalbumin and recombinant parvalbumin (rCyp c1.01). Sera were chosen from nine fish-processing workers in South Africa who had tested positive for specific IgE against pilchard (*Sardina pilchardus*). Mice sensitized with raw fish recognized different allergens to those sensitized with cooked fish.

Fish Allergens

Fish species and seafood products that cause allergy can be classified based on cluster analysis of immunoglobulin reactivities of children into four groups, consisting of (1) salmon, sardine, and mackerel, (2) cod and tuna, (3) octopus and squid, and (4) crab and shrimp [63].

The allergen in fish, known as Allergen M or Gad c 1, was first identified in the Atlantic cod (*Gadus morhua*) in 1969 [64]. It was one of the first food allergens identified. This allergen consists of 113 amino acids and a glucose molecule, with a molecular weight of about 12 kDa. It belongs to a family of parvalbumins, a group of calcium-binding proteins which are present in high amounts in white muscles of lower invertebrates [65] and in lower amounts in fast twitch muscles of higher vertebrates [66]. Lindstrom et al. [67] purified parvalbumin in the Atlantic salmon (*Salmo salar*) and confirmed its allergenicity, and van Do et al. [68] further confirmed this finding. Parvalbumin has also been characterized as the allergen in horse mackerel [69] and carp [70, 71]. Other identified fish allergens are TM and arginine kinase; however, parvalbumin represents the major cross-reactive fish allergen [72–75]. Several studies have published the identified and characterized allergens in

temperate fish and seafood from Asian countries. The most extensively studied allergen in the temperate fish is Gad c 1 (belonging parvalbumins) which is the major allergen of concern [76]. Studies on the other temperate fish have shown that parvalbumin constitutes the major cross-reactive fish allergen [2, 77].

Table 2 shows the summary of allergenic protein of seafood identified in different countries. Misnan et al. [78] determined the IgE-binding proteins and major allergens of narrow-barred Spanish mackerel (*Scomberomorus commerson* Lacepede) from Malaysia. Uncooked fish samples showed 26 protein bands in the range of about 11 to >175 kDa, while the cooked fish produced fewer protein bands. Immunoblotting revealed 17 IgE-binding bands, ranging in molecular weight from 11 to 151 kDa. Two components with molecular weight of about 50 and 42 kDa showed the highest frequency of IgE-binding (62.2% and 51.4%, respectively) and were identified as the major allergens of this fish allergy. Other IgE-binding proteins including a protein at 12 kDa with equivalent size to parvalbumin were identified as the minor allergens. Misnan et al. [78] also identified the IgE-binding proteins and major allergens of red snapper (*Lutjanus argentimaculatus*) and golden snapper (*Lutjanus johnii*) from Malaysia. Both species of fishes had similar protein profiles. Their study showed that, in cooked extracts, several protein bands in the range of about 40 to 90 kDa, which were present in the uncooked extracts, appeared to be denatured and formed high molecular weight complexes. The immunoblotting of golden snapper and red snapper revealed 16 and 15 various IgE-binding bands, in the range of 151 to 1211 kDa, respectively. A 51 kDa protein was identified as a major allergen for both fishes. A 46 kDa protein was also demonstrated as a major allergen in golden snapper, and a 42 kDa protein was also seen as a major allergen in red snapper. A heat-resistant protein of 12 kDa which is equivalent in size with fish parvalbumin was demonstrated only as minor allergen for both fishes. Study by Misnan et al. [79] on tuna fish (*Thunnus tonggol*) from Malaysian water demonstrated that enolase and triose phosphate isomerase are the major allergenic component of this species of fish. Their study also detected a heat-resistant protein at 12 kDa as parvalbumin, which is similar as Sal s 1. However, this protein was only seen as a minor allergen for this fish.

A study from Singapore showed that parvalbumin was found in the white muscle of tuna and absent in the red muscle. They revealed that this protein was unequally distributed, with ventral white muscle containing slightly more parvalbumin than the dorsal white muscle. The amount of parvalbumin decreased from the rostral region to the caudal region [80]. Another study on four species of tropical fish (threadfin, pomfret, Indian anchovy, and tengiri (mackerel) from Singapore waters showed that parvalbumin

Table 2 Seafood allergens identified in different regions

Source of allergen	MW (kDa)	Identity	Country	Reference
Narrow-barred Spanish mackerel	11–151	IgE-binding proteins	Malaysia	[78]
Red snapper	40–90			[78]
Golden snapper	40–90			[78]
Tuna	12	Sal s 1		[79]
Swimming crab, red crab	15–138	IgE-binding proteins		[79]
Tuna	12	Parvalbumin	Singapore	[80]
Threadfin, pomfret, Indian anchovy, mackerel	12	Parvalbumin		[81]
Horse mackerel	10,500	Tra j 1	Japan	[69]
Yellowfin tuna	46	–		[82]
Mackerels	11	Parvalbumin		[84]
Fish	94	AAP94279		[85]
Horse mackerel, Pacific mackerel	12	Parvalbumin		[86]
Shrimp	16.5, 40	IgE binding protein		[97]
	–	Tropomyosin		[98]
American lobster, black tiger prawn	37	Tropomyosin		[100]
Black tiger shrimp	20	SCP		[101]
Pacific flying squid	38	Tod p 1		[125]
Gastropod	35	Tur c 1		[126]
Crab	34	Cha f 1	China	[102]
Lobster	34	Pan s I		[103]
American lobster	60	Hom a I		[103]
Chinese mitten crab	62	GST–TM		[104]
Shrimp	39–86	Par f I		[106]
Abalone, scallop, mussel	38	Tropomyosin		[128]
Crustaceans and mollusks	38	Tropomyosin		[129]
Shrimp	34	Met e I	Hong Kong	[105]
Crustacean	14–70	Pen m 2	Taiwan	[108]
Pacific pilchard	10–13	Parvalbumin	Africa	[27]
Yellowtail, anchovy, hake	24–38	Parvalbumin		
Cooked pilchard	36	Parvalbumin, recombinant Cyp c1.01		[28]
Abalone	49	Hai-m-1		[18]
Alaska pollack	12	Parvalbumin, The c 1	Germany	[87]
Carp	11	Cyp c 1.01 and Cyp c 1.02	Austria	[71]
<i>A. simplex</i>	14	Ani s 9	Spain	[88]
	–	Ani s 2, Ani s 3	Italy	[89]
North Sea shrimp	2–28	TM, AK, SCP, MLC, TnC, TIM	Switzerland, Spain, Germany and Sweden	[109]
Shrimp	20	MLC	Spain	[110]
	20	Lit v 4.0101		[111]
	34	Met e I	USA	[105]
Catfish, cod, snapper, tuna	12–45	Gad c I		[114]
Shrimp	43–284	Pen a 1		[115]
	–	Pen a 1, Per a 7, Der p 10		[116]
Shrimp and scallops	21–42	–		[33]
Pacific white shrimp	40	Lit v 2	Mexico	[117]

is the major allergen of these tropical fish. These parvalbumins are cross-reactive with Gad c 1 which was also

clinically evident because most fish-allergic children in this study had clinical reactions to more than one fish [81].

Shiomi et al. [69] studied the allergenicity of five species of fish (horse mackerel *Trachurus japonicus*, Pacific mackerel *Scomber japonicus*, bigeye tuna *Thunnus obesus*, chum salmon *Oncorhynchus keta*, and walleye pollack *Theragra chalcogramma*) from Japan. They let the white muscle extracts of fishes to react with the IgE antibodies in one patient serum. The highest reaction was given by the horse mackerel extract and the lowest reaction by the bigeye tuna extract. Bigeye tuna was the only positive sample as analyzed using another patient serum. A heat-stable allergen (named Tra j 1) with a molecular weight of 10,500 was isolated in the horse mackerel. Tra j 1 was rich in Ala, followed by Asx and Lys, but lacked of Cys (half), His, and Trp. Furthermore, it showed an ability to bind to the monoclonal antibody against carp parvalbumin. From these physicochemical and immunological properties, they identified Tra j 1 as parvalbumin of the horse mackerel.

Yamada et al. [82] characterized IgE-binding components of Yellowfin and Albacore tuna fish from Japan. They identified a specific protein with a molecular weight of approximately 46 kDa that is present in Yellowfin tuna, but absent in Albacore. Only defatted, lyophilized tuna fish extracts were able to induce histamine release from sensitized basophils, although IgE-binding components were detected in fresh raw, fresh cooked, and canned tuna fish preparations. Their studies indicated that patient sera may contain different tuna fish species IgE-specific antibodies directed against unique species-specific allergens present in Yellowfin and Albacore tuna fish. They assumed that the extracts may contain specific allergenic components from both Albacore and Yellowfin to cover the epitope heterogeneity observed in sera from patients developing IgE antibodies against tuna fish. Fish was reported as one of the most common causes of food allergy in Japan. An investigation conducted by the Japanese government in 1997 showed that fish was ranked second among various causes of food allergy for adults and that approximately 20% of food-allergic adults in Japan were sensitive to fish [63]. A high molecular weight allergen has been detected in bigeye tuna from Japan. Analyses by enzyme-linked immunosorbent assay (ELISA) showed that the high molecular weight allergen was contained in the myostomal protein fraction which identified to be collagen based on the results of sodium dodecyl sulfate polyacrylamide gel electrophoresis (SDS-PAGE), immunoblotting, and amino acid analysis. The bigeye tuna collagen almost completely inhibited the IgE reactivity to the heated extracts from five species of fish, suggesting that collagen is commonly allergic regardless of fish species. However, no antigenic cross-reactivity was observed between collagens from fish and other animals [83]. Hamada et al. [84] purified parvalbumin (a possible candidate for the major allergen) from the white muscle of three species of

mackerels (*S. japonicus*, *S. australasicus*, and *S. scombrus*) from Japan. All the purified preparations from three species gave a single band of about 11 kDa and were clearly identified as parvalbumins by analyses of their partial amino acid sequences. Using sera from fish-allergic patients, they proved that parvalbumin was the major allergen in common with the mackerels. Hamada et al. [84] evaluated fish muscle collagens for their reactivity with IgE in fish-allergic Japanese patients and antigenic cross-reactivity. Their study demonstrated that some Japanese fish-allergic patients have specific IgE to fish muscle collagen and that fish muscle collagen is a cross-reactive allergen among various species of fish.

Kondo et al. [85] claimed that parvalbumin is not responsible for cross-reactivity. For the first time, they reported cross-reactivity between fish species by a protein other than parvalbumin. Their analysis showed the 94 kDa protein with 78% identity with the amino acid sequence of transferring (AAP94279) from *Pagrus major*. They pointed that a patient with an anaphylactic reaction to one fish species can experience an anaphylactic reaction to another caused by a cross-reacting allergen other than parvalbumin. Kobayashi et al. [86] compared the allergenicity and allergens between white and dark muscles of five species of fish from Japan. Patient sera showed less reactivity to the heated extract from the dark muscle than to that from the white muscle. Same parvalbumin molecule was observed in both white and dark muscles of either horse mackerel or Pacific mackerel but the parvalbumin contents were four to eight times lower in the dark muscle than in the white muscle. Therefore they concluded that the fish dark muscle is less allergenic than the white muscle.

The study by Beale et al. [27] identified oligomeric forms of parvalbumin in five highly consumed fish species (pilchard *S. sagax*, anchovy *E. encrasicolus*, hake *M. merluccius*, snoek *T. atun*, and yellowtail *S. lalandi*) in Southern Africa. Purification of parvalbumin from five fish species showed the presence of oligomers in homogenous extracts using a commercial monoclonal anti-parvalbumin antibody. A highly cross-reactive allergenic isoform of parvalbumin was identified from Pacific pilchard which was characterized at molecular level. Isoforms varied between approximately 10–13 kDa. Sera from several subjects also displayed IgE reactivity to 24 and/or 38 kDa proteins in yellowtail, anchovy and hake crude extracts which were assumed to be oligomers of parvalbumin due to the comparable positions of dimeric and trimeric parvalbumin.

Recently van der Ventel et al. [28] identified the allergenic proteins in raw and/or cooked pilchard (*S. pilchardus*) from South Africa. A 36 kDa protein identified as glyceraldehyde-3-phosphate dehydrogenase, which was also recognized by sera from mice and fish processing workers. Natural pilchard parvalbumin and recombinant

Cyp c1.01 both caused airway reactions after intranasal challenge; however, specific immune responses to the two parvalbumins were different.

van Do et al. [87] studied on parvalbumin, from Alaska pollack in comparison with codfish allergen. Alaska pollack was purchased from Norway market as frozen fillet produced by Germany. Parvalbumin from Alaska pollack, designated The c 1, was purified; it showed two distinct fractions which had similar IgG and IgE binding capacities. cDNA cloning revealed two isotypic parvalbumin transcripts in pollack muscle. Recombinant parvalbumins of pollack exhibited low IgG and IgE binding capacities, in contrast to the native counterparts, which were almost as potent as cod Gad c 1. The allergenicity of The c 1 was assayed by ELISA inhibition, and compared to cod, the concentration required for obtaining 50% ELISA inhibition (C 50%) was only 18% higher for The c 1.

Swoboda et al. [71] studied on fish allergens in Austria. They have constructed an expression cDNA library from carp (*Cyprinus carpio*) muscle in phage λ gt11. They used serum IgE from a fish allergic patient to isolate 33 cDNA clones which coded for two parvalbumin isoforms (Cyp c 1.01 and Cyp c 1.02) with comparable IgE-binding capacities. Their study showed that both isoforms represent calcium-binding proteins that belonged to the β -lineage of parvalbumins. The Cyp c 1.01 cDNA was overexpressed in *Escherichia coli*, and rCyp c 1.01 was purified to homogeneity. rCyp c 1.01 represented a folded protein with a molecular mass of 11,416 Da which reacted with IgE from all 60 fish-allergic patients tested. This protein induced specific and dose-dependent basophil histamine release and contained most of the IgE epitopes (70%) present in natural allergen extracts from cod, tuna, and salmon. They suggested that this protein can be used to identify patients suffering from IgE-mediated fish allergy. This study also showed therapeutic potential of rCyp c 1.01, where rabbit Abs raised against rCyp c 1.01 inhibited the binding of IgE in fish-allergic patients to rCyp c 1.01 between 35% and 97%. Depletion of calcium strongly reduced IgE recognition of rCyp c 1.01. The results suggest that it will be possible to develop strategies for immunotherapy for fish allergy that are based on calcium-free hypoallergenic rCyp c 1.01 derivatives.

A study on allergenic effect of *A. simplex* identified a new allergen Ani s 9-cDNA in this parasite [88]. The complete cDNA for Ani s 9 was obtained by RACE-PCR, cloned and sequenced. Expression of recombinant allergen was performed in *E. coli*. Immunodetection and immunoblot inhibition assays tests were carried out with sera from *Anisakis* allergic patients from Spain. This study indicated that recombinant Ani s 9 (rAni s 9) is a protein of 147 amino acids, which is located as a 14 kDa band present in a crude extract of the parasite. This allergen is heat-stable and

is present in excretory/secretory products. Ani s 9 belongs to the SXP/RAL-2 family and shares amino acid sequence identity of 60% with As-14, an *Ascaris suum* allergen. Of 36 *Anisakis*-allergic patients, five (13.8%) were positive to rAni s 9 and natural Ani s 9 by immunodetection.

Another study by Guarneri et al. [89] from Italy reported another allergens assumed to be cross-reactive with Ani s 2 (paramyosin) and Ani s 3 (TM) of *A. simplex*. They identified a number of proteins belonging to various organisms, which are significantly similar to and therefore are likely to cross-react with Ani s 2 and Ani s 3. They introduced the presence of binding motifs of HLA DRB1*0404 in Ani s 2, Ani s 3, and homolog proteins as support to their hypothesis.

The research by Espineira et al. [90] developed a rapid and sensitive method for the detection of anisakids in seafood based on PCR. Their method allows detecting the presence of anisakids in fish and determining the particular anisakid species. They studied on larvae of *Anisakis*, *Pseudoterranova* spp., *Hysterothylacium* spp., and *Contracaecum* spp. isolated from fish samples obtained from different fish markets and shops in Spain. That protocol allows the simultaneous detection and identification of the most important anisakid species present in fish products. This method can be applied to all kinds of processed products including those undergoing intensive processes of transformation, for instance, canned foods. They proposed rapid, robust, highly sensitive, and readily adaptable method in routine molecular diagnostic laboratories.

Later, Herrero et al. [91] developed a TaqMan-LNA probe real-time assay which can simultaneously detect the most important anisakids species present in fish and seafood products. For the validation of method developed, 20 fish and cephalopod samples were experimentally contaminated with anisakid. It was checked that, in cases where any anisakids species was present, it was detected because the Ct was always less than 35 and did not produce any case false negatives. This method can also be applied to all kinds of processed products including those undergoing intensive processes of transformation, for instance, canned foods.

Crustacean Allergens

Crustaceans such as shrimp, lobster, and crab have long been known to be the most common allergic food items among seafood. Isolation of shrimp allergens by biochemical methods was first reported in the 1980s [92, 93]. TM, a heat-stable muscle protein, is the major allergen in shellfish and seafood, with highly homologous proteins being found in the commonly edible crustaceans. These homologies are responsible for the cross-reactive allergies observed

between various types of seafood, such as shrimps, lobsters, crab, squid, and abalone, and inhalant insect allergens including those from cockroaches. Two main linear IgE-binding sites have been identified in the shrimp allergen, Pen i 1, in the N- and C-terminal regions. The first two residues of the C-terminal epitope appear to be crucial for IgE binding and are not found in vertebrate TM. As a consequence of the lack of homology in the IgE epitopes, there is no IgE cross-reactivity between crustacean and animal muscle TMs. In addition to being found in cooked meat, the allergen also leaches into cooking water [94].

Sheah-Min and Choon-Kook [95] investigated the relevance of specific IgG4, along with IgG and IgE antibodies to two common food allergens in Malaysia. They found that the elevation of specific IgE or IgG4 is associated with shrimp and crab allergies but the elevation of specific IgG is not associated with either allergy. Misnan et al. [79] characterized the IgE-binding proteins and major allergens of blue/swimming crab (*Portunus pelagicus*) and red crab (*Charybdis japonica*) from Malaysian waters. The protein profiles were similar in both species of crab. The uncooked extracts of both crab produced 19 protein bands in the range of 15 to 138 kDa. Several protein bands between 17 to 25 kDa and 50 to 71 kDa which were present in the uncooked extracts appeared to be denatured in the cooked extracts. The immunoblotting of blue and red crab revealed 14 and 15 various IgE-binding proteins in the range of 24 to 138 kDa, respectively. The most common IgE-binding proteins were identified in the range of 34 to 46 kDa. Two proteins (34 and 36 kDa) were identified as major allergen for both crab species, which were similar in size with TM, the main major allergen, and were responsible in the majority of allergic reactions to various seafood species including crab.

Temporal patterns of first exposure of infants to fish and shellfish are unique to the Asian diet. Shellfish are a major sensitizing food source in Singaporean children, especially in allergic rhinitis patients sensitized to cockroaches [9]. Perez-Macalalag et al. [96] studied the effect of vinegar on shrimp allergenicity, based on skin test results of shrimp-allergic pediatric patients in the Philippines. Results indicated that vinegar soaking prior to cooking can reduce shrimp allergenicity.

A detailed comparison between atopic and non-atopic patients with adverse reactions to shrimp was studied in Japan [97]. The level of specific IgE to shrimp was higher in atopic patients than nonatopic patients ($p < 0.05$). Symptoms, SPT results, and major allergens involved were similar in atopic and nonatopic patients. They reported that the 16.5 kDa protein had the highest frequency of IgE binding followed by the 40 kDa protein in these patients. Patients who had binding to the 16.5 kDa protein had either positive (25% raw/31% cooked) or negative (13% raw/cooked) CAP-FEIA-

RAST, while patients who recognized the 40 kDa protein all had positive (31% raw/19% cooked) CAP-FEIA-RAST. The 16.5 kDa protein was the most frequent protein identified regardless of CAP-FEIA-RAST results, while the 40 kDa protein was only present in patients with positive CAP-FEIA-RAST. Therefore, they concluded that 16.5 kDa protein may be an important allergen that was clinically relevant in both atopic and nonatopic patients with adverse reactions to shrimp.

Byun et al. [98] studied the application of food irradiation technology as a method for reducing shrimp allergy without adverse effects. The study showed that the ability of the immunoglobulin E of patients allergic to shrimp to bind to irradiated heat shock protein (HSP) was dose-dependently reduced. The amount of intact HSP in an irradiated solution was reduced by gamma irradiation, depending on the dose. The binding ability of immunoglobulin E to allergens in the extracts from irradiated shrimp decreased. In another study, Byun et al. [98] used shrimp TM as model food allergens to evaluate the application of food irradiation technology to reduce food allergy. Their study showed that epitopes on the allergens were structurally altered by radiation treatment. They introduced a new method to reduce allergenicity of shrimp.

Shrimp is known to be the most common causative agent in seafood allergy. Patients with shrimp allergy often exhibit allergic symptoms to a variety of seafood such as crabs and clams [50]. Motoyama et al. [99] reported allergenicity and allergens in amphipods mixed in nori (the red alga *Porphyra yezoensis*) in Japan. Sera from crustacean-allergic patients reacted to extracts from amphipod samples, although less potently than to the extracts from decapods. They identified a 37 kDa protein to be the major allergen in amphipods which they introduced as amphipod TM. A study on allergen in decapod crustaceans, which is used as delicacy in Japan, identified a 37 kDa protein in two species of decapods (American lobster *Homarus americanus* and black tiger prawn *P. monodon*) and two species of barnacles (acorn barnacle *Balanus rostratus* and goose barnacle *Capitulum mitella*) [100]. In immunoblotting, the 37 kDa protein was found to react with monoclonal antibodies against American lobster TM and therefore identified as TM. The patient sera reacted to TMs from both decapods and barnacles and the reactivity was eliminated by preincubation with American lobster TM. This showed that barnacle TMs are allergens cross-reactive with decapod TMs. Shiomi et al. [101] found a new allergen of 20 kDa during purification of arginine kinase from black tiger shrimp *Penaeus monodon* from Japan. The 20 kDa protein was purified from black tiger shrimp and identified as a sarcoplasmic calcium-binding protein (SCP). They pointed that distribution of IgE-reactive SCP was probably limited to shrimp and crayfish.

The first study on the molecular characterization of crab allergens from China identified a 1-kb cDNA designated as Cha f 1. Expression of Cha f 1 produces a 34 kDa recombinant protein reactive to the IgE antibodies from patients with crab allergies. It demonstrated marked homology to the shrimp TM Met e 1. Nucleotide and amino acid comparison shows that this protein is the crab TM [102]. Leung et al. [103] identified and characterized lobster allergens from China. Expression and sequencing of this DNA clone showed that it had an open-reading frame of 274 amino acids, coding for a 34 kDa protein designated as Pan s I. In addition, they also found that muscle TM from the American lobster (*H. americanus*), coined Hom a I, was also recognized by IgE from patients with crustacean allergies. The deduced amino acid sequences of Pan s I and Hom a I, which was the first identified lobster allergens, showed significant homology to shrimp TM. Their results suggested that patients with allergic reactions to crustaceans have common and possibly cross-reactive IgE-reactive epitopes in lobster and shrimp. TM from Chinese mitten crab was purified and its genes were amplified by Liang et al. [104] and Leung et al. [105]. Their results showed that the three TMs share high homology to TMs from other crustaceans. The expressed protein of Chinese mitten crab TM gene revealed a band of about 62 kDa on SDS-PAGE, suggesting the successful expression of glutathione *S*-transferase (GST)–TM fusion protein. The expressed fusion protein reacted positively with sera from patients with crustacean allergy, which indicated that TM was a major allergen of Chinese mitten crab.

Leung et al. [105] studied the primary structure of the major heat-stable allergen of shrimp from Hong Kong. They proved that serum antibodies from patients with shrimp allergy demonstrated positive IgE reactivity by immunoblotting to a protein encoded by the clone Met e I. The nucleotide sequence of this cDNA clone showed an open-reading frame of 281 amino acid residues, coding for a protein of 34 kDa. Their study showed that Met e I is highly homologous to multiple isoforms of TM. Lin et al. [106] identified six allergenic components of the shrimp (*Parapenaeus fissurus*) from China which their molecular weight ranged from about 39 to 86 kDa. These proteins showed IgE-binding activity and were identified as allergens of the shrimp. The component with a molecular weight of about 39 kDa showed the highest frequency of IgE binding (70%) and was considered to be one of its major allergens. They identified and characterized a 39 kDa major allergen from the shrimp as Par f I.

A study on the serum samples of allergic patients from Taiwan exhibited that the competitive inhibition of IgE binding between shrimp and crab allergens was higher than those between either shrimp or cockroach or between crab and cockroach. In addition, the results of immunoblotting

were consistent with those of quantitative-competitive inhibition tests [107]. A novel allergen from *Penaeus monodon*, designated Pen m 2, was identified using sera from subjects with shrimp allergy in Taiwan [108]. Comparison of the Pen m 2 sequence with known protein sequences revealed wide similarity with arginine kinase (EC 2.7.3.3) from crustaceans. It showed to have arginine kinase activity and to react with serum IgE from shrimp allergic patients and induce immediate type skin reactions in sensitized patients. Therefore Pen m 2 was identified as a novel cross-reactive crustacean allergen.

Recently, Bauermeister et al. [109] generated a comprehensive panel of North Sea shrimp (*Crangon crangon*) allergens and the IgE-binding diversity to these allergens among 31 shrimp-allergic subjects from different places in Europe (Switzerland, Spain, Germany and Sweden). Six recombinant crustacean proteins (TM, AK, SCP, a novel MLC, troponin C (TnC), and triosephosphate isomerase (TIM) bound IgE in ImmunoCAP were identified. Specific IgE to at least one of these single shrimp allergens was detected in 90% of the study population, thus the in vitro diagnostic sensitivity was comparable to that of shrimp extract (97%). In 75% of the subjects, the combined technical sensitivity was similar to or greater with single shrimp allergens than with natural shrimp extract.

Ayuso et al. [110] identified relevant crustacean allergens for use as diagnostic and safe immunotherapeutic agents for subjects with shellfish allergy. Sera were collected from 38 Spanish patients with shrimp allergy with histories of immediate allergic reactions after the ingestion of shrimp and increased serum IgE levels to shrimp. One-dimensional and 2-dimensional electrophoresis of shrimp extracts were followed by IgE immunoblotting. Protein identification was done and a cDNA library was generated from white pacific shrimp (*Litopenaeus vannamei*) and screened. Full-length cDNA clones were isolated from the library and sequenced. Recombinant protein was expressed and tested with sera from patients with shrimp allergy. Immunoblotting demonstrated IgE binding to a 20 kDa shrimp protein by 55% of 38 sera. Screening of the shrimp cDNA library resulted in isolation of a novel protein cDNA. An amino acid sequence of a new allergenic shrimp protein with high similarity to Bla g 8 was identified. Recombinant protein was recognized by 17 patients, confirming the allergenicity of shrimp MLC. Later in 2009, Ayuso et al. [111] characterized some new allergens of shrimp Lit v 4.0101, an SCP. They used 52 adults and children with a history of immediate allergic reactions to shrimp and elevated serum IgE to shrimp. Immunoblotting demonstrated IgE binding by 31 of 52 (59.6%) of the sera to a 20 kDa shrimp protein. They isolated the amplified and sequenced cDNA encoding SCP. Recombinant SCP was recognized by serum IgE from 38.4% subjects, of whom 85% were children. They concluded that

this allergen is of particular importance in the pediatric population.

Hoffman et al. [112] identified the major heat stable allergen of shrimp. Serum from an American patient who had experienced several episodes of anaphylaxis after eating shrimp was used to monitor the isolation of a major allergen from shrimp, which was then tested with sera from ten other shrimp-reactive patients. The allergen was isolated and the purity of the allergen was established by crossed immunoelectrophoresis against rabbit and guinea pig antisera. Using the RAST with 11 allergic sera, the allergen gave a strong correlation with whole cooked shrimp extract and raw shrimp extract. The allergen was a potent inhibitor of RAST to both cooked and raw shrimp.

In order to identify the mechanism of seafood hypersensitivity at the molecular level, the primary structure of the major heat-stable allergen of shrimp was determined by cloning, expression, nucleotide sequencing [105]. They constructed a cDNA library from the shrimp *M. ensis* in λ gt 11. Then the library was screened with sera from patients with hypersensitivity reactions to shrimp and a positive IgE-reactive clone, designated as Met e I was identified. Serum antibodies from American patients with shrimp allergy demonstrated positive IgE reactivity by immunoblotting to a protein encoded by the clone Met e I. The nucleotide sequence of this cDNA clone revealed an open-reading frame of 281 amino acid residues, coding for a protein of 34 kDa. Comparison of the Met e I amino acid sequence with the Genbank database showed that Met e I is highly homologous to multiple isoforms of TM.

Witteman et al. [113] described a monoclonal antibody to *D. pteronyssinus* that cross-reacts with an IgE-binding antigen present in insects, crustacean (e.g., shrimp), and other invertebrates. Their study showed that this monoclonal antibody presumably recognizes TM. TM was shown to be involved in cross-reactivity between mite, shrimp, and insects in shrimp-allergic patients.

James et al. [114] compared the binding of pediatric and adult fish-allergic patient IgE antibodies to fish proteins. Clinical histories of fish allergy were confirmed by prick skin tests, RAST, and blinded oral food challenges. The patients included five American children with severe allergic reactions to catfish (4/5), cod (1/5), and tuna (1/5) and five adults with severe allergic reactions to catfish (5/5), cod (2/5), snapper (3/5), and tuna (2/5). The multiple fish proteins identified ranged from 12 to 45 kDa. A major protein (12.5 kDa) was present in all fish extracts except for raw tuna. The study showed that the major IgE binding was to the 12.5 kDa protein from catfish, cod, and snapper. The immunoblot with tuna using serum from a pediatric patient with isolated tuna anaphylaxis revealed an IgE binding protein band at 40 kDa. Preincubation of serum samples from two separate fish-allergic patients inhibited IgE

binding to the 12.5-kDa fish protein. Their result revealed that pediatric and adult fish-allergic patients have similar in vitro IgE binding to a 12.5 kDa protein from fish extracts. This protein was immunochemically similar to Gad c I which is the major allergen in cod.

Ayuso et al. [115] studied the relationship between protein structure and allergenicity of the major shrimp allergen Pen a 1 (TM). They identified the IgE-binding regions of Pen a 1 and compared these regions with homologous sequences in other allergenic and nonallergenic TMs. They synthesized the overlapping peptides and tested them for IgE antibody reactivity with sera from 18 shrimp-allergic subjects from the USA to identify the IgE-binding regions of shrimp TM. All of the five major IgE-binding regions identified were 15–38 amino acids long. The major IgE-binding regions identified were: region 1: Pen a 1 (43–57); region 2: Pen a 1 (85–105); region 3: Pen a 1 (133–148); region 4: Pen a 1 (187–202), and region 5: Pen a 1 (247–284). There were no substantial differences in amino acid group composition in the five IgE-binding regions compared to the whole molecule. Sequence identities and similarities of the Pen a 1 IgE-binding regions with homologous regions of allergenic arthropod TMs were as high as 100%. The identities and similarities with homologous vertebrate sequences ranged from 36% to 76% and from 53% to 85%, respectively. This study showed a structural basis for cross-reactivity of allergenic TMs.

Ayuso et al. [116] identified IgE-binding epitopes of shrimp allergens, namely, Pen a 1, Per a 7, and Der p 10, and assessed their cross-reactivity. Sera from five shrimp allergic subjects from US were tested for IgE reactivity to three sets of overlapping synthetic peptides, 15 residues long, offset of 6, spanning the entire length of Per a 7, Pen a 1, and Der p 10. Shrimp-allergic subjects recognized 27 IgE binding Pen a I peptides with maximal intensity; homologous sequences from 19/27 Pen a 1 peptides were also recognized in Per a 7 or Der p 10 by shrimp-allergic subjects. Pooled shrimp-allergic sera recognized 27 IgE-binding peptides in Pen a 1. Homologous sequences from 70% or more of the identified epitopes in one TM (Per a 7 or Pen a 1) were also recognized in the other arthropod TMs (Per a 7, Pen a 1, Der p 10). Similar IgE-binding epitopes in Per a 7, Der p 10, and Pen a 1 explained the in vitro cross-reactivity among arthropods, and could be of clinical relevance, in the induction of clinical symptoms with different arthropods in subjects sensitized to vertebrate TM.

García-Orozco et al. [117] studied on the purification, molecular cloning, and immunological analyses of allergens from the Pacific white shrimp (*L. vannamei*) produced in Latin America (Mexico). A 40 kDa protein was purified and identified as arginine kinase and its cDNA of 1.4 kb

encoded a 356 amino acid protein. The obtained arginine kinase was recognized by IgE in serum from shrimp-allergic individuals from Mexico. This allergen has a 96% identity to Pen m 2 from *Penaeus monodon*; they named it Lit v 2.

Following the case of a restaurant seafood handler in the USA with IgE-mediated occupational asthma and contact urticaria to both shrimp and scallops, Goetz and Whisman [118] conducted a research to investigate cross-reactivity of shrimp and scallops. SDS-PAGE of shrimp boiling water and distillate showed similar protein patterns. SDS-PAGE and immunoblot demonstrated prominent protein allergens for shrimp boiling water at 21, 26, and 35–38 kDa; for raw shrimp at 26 and 38 kDa; for scallops boiling water at 20, 35–39, and 42 kDa; and for raw scallops at 36–38 and 41 kDa. Significant inhibition of the 35- to 39-kDa band of each shrimp and scallops extract was demonstrated on immunoblot inhibition by seafood of the opposite phylum. IgE ELISA inhibition demonstrated 17–28% inhibition of shrimp by scallops and scallops by shrimp. This study concluded that seafood allergens aerosolized during food preparation are a source of potential respiratory and contact allergens. Shrimp and scallops demonstrated significant cross-reactivity.

Mollusk Allergens

The mollusks commonly consumed in Asia include members of class Gastropoda (e.g. limpet and abalone), class Bivalvia (e.g. scallop, clam, mussel, and oyster) and class Cephalopoda (cuttlefish, squid, and octopus). There have been a number of reports on allergies to mollusks including allergies to snail [119], abalone [120], limpet [121, 122], cuttlefish [123], and squid [124].

In Japan, squid is important seafood, and some patients with food allergies are sensitive to squid. For the first time, Miyazawa et al. [125] characterized squid allergens and isolated a major allergen from the Pacific flying squid (*Todarodes pacificus*) and compared it with shrimp (*P. orientalis*) major allergen from Japan. The isolated squid allergen was a 38 kDa, heat-stable protein. Cross-reactivity between major squid and shrimp allergens was demonstrated with sera from patients allergic to squid or shrimp or with allergen-specific monoclonal antibodies. The amino acid sequence analysis of the major squid allergen demonstrated a marked homology with TM from blood fluke planorbid (*Biomphalaria glabrata*), which is a common vector snail of *Schistosoma mansoni*. They identified this 38 kDa protein as squid muscle protein TM and called it Tod p 1. Ishikawa et al. [126] identified the major allergen (Tur c 1) of gastropod, *Turbo cornutus*, from Japan. Their analysis proved that Tur c 1 was tropomyosin,

which was same with other mollusk and crustacean allergens. Their results also suggested that Tur c 1 had an IgE-binding epitope in the C-terminal which was dissimilar to those proposed for Cra g 1 (the oyster allergen) and Pen i 1 (shrimp allergen). Ishikawa et al. [126] also isolated the major allergen (Cra g 1) of oyster, *Crassostrea gigas*, from Japan. Cra g 1 was identified as TM. Their results suggested that Cra g 1 had an IgE-binding epitope in the segment 92–105 (IQLLEEDMERSEER) which was dissimilar to those of the major allergen (TM) from the shrimp *P. indicus*. TM, which is the major allergen of shellfish, was prepared from scallops collected from Japan local markets and reacted with four reducing sugars to investigate the effect of the Maillard reaction on the allergenicity of TM. The IgE-binding ability of TM increased significantly with the progress of the reaction with glucose, ribose, and maltose, but not with maltotriose. The allergenicity was increased at the early stage of the Maillard reaction, and the trend of the effect depended on the type of reducing sugar used. 2,4,6-Trinitrobenzenesulfonic acid treatment of the lysine residues in TM showed that the protein surface charge resulting from the Maillard reaction had no effect on the enhancement of the allergenicity. They concluded that the change in the allergenicity would be closely related to the structural change caused by the Maillard reaction [127].

Chu et al. [128] amplified the complementary DNAs encoding TMs of the abalone *Haliotis diversicolor*, the scallop *Chlamys nobilis*, and the mussel *Perna viridis* from China. Their analysis showed that recombinant proteins of abalone, scallop, and mussel TM were reactive to serum IgE antibodies from subjects allergic to shellfish but not to nonallergic controls. Nucleotide and amino acid sequences of abalone, scallop, and mussel TMs are highly similar (mostly >55%) to those of crustacean allergens identified as TMs. Recombinant TMs from the three mollusks were able to remove serum IgE reactivity against the 38 kDa TM of the organisms. Therefore, they identified TM as the major allergen among various common edible mollusks. Leung et al. [129] studied the mechanism of cross-reactivity between mollusks and other crustaceans in shrimp sensitivity in Hong Kong. A 38 kDa protein was identified as TM and shown to share immunodominant epitopes among all species of crustaceans and mollusks tested by specific absorption studies. Moreover, sera from all patients with shrimp allergy demonstrated IgE reactivities against grasshopper, cockroach, and fruit fly but not chicken or murine muscle. The allergic epitopes on TM were conserved among invertebrates including not only shellfish but also insects. They suggested that persons sensitive to shrimp should undergo further study for potential cross-reactive inhalant or ingested insect sensitivity.

In the study by Lopata et al. [18] the allergenic components of South African abalone (*Haliotis midae*)

were identified. They reported that abalone allergens are heat-stable proteins with molecular weights of 38 and 49 kDa, which the 49 kDa IgE-binding protein has been designated as Hai-m-1.

Conclusion

Allergic reactions to seafood are a common cause of food allergy in many regions of the world where fish is a major source of protein. There are various studies conducted on the epidemiology and clinical characteristics of seafood allergy in different parts of the world, and some of the fish and seafood allergens unique to this region have been characterized. However, such studies are lacking from many regions with high fish and seafood consumption such as Indonesia, Cambodia, Laos, Myanmar, and Vietnam, some parts of the USA (e.g., California), northern Europe (e.g., France), Scandinavia, Australia, and New Zealand. Furthermore, the published data are mostly from small groups of populations, which large-scale population-based epidemiological studies need to be performed. Additionally, there are limited investigations on possible cross-reactivity between different species of fish and seafood and other foods.

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